Table 13

Summary of Baseline Observations for "Efficacy Patients", by Center and Treatment Group

		HR, bpm	SBP, mm Hg	DBP, mm Hg	MAP, mm Hg	RPP	
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	N
Center[a]	Group						
3 & 4	Esmolol	80.2 3.8	154.4 4.1	80.5 2.9	105.2 3.5	12.4 0.7	19
	Placebo	82.8 3.5	144.9 5.9	81.5 3.3	102.6 3.8	12.1 0.8	19
	Pooled	81.5 2.6	149.6 3.6	81.0 2.1	103.9 2.3	12.2 0.5	38
6	Esmolol	70.7 5.3	130.8 5.1	72.7 4.1	92.1 4.3	9.4 1.0	13
	Placebo	74.9 4.1	129.6 6.9	72.1 3.1	91.3 3.9	9.7 0.8	12
	Pooled	72.7* 3.3	130.3 4.2	72.4 2.0	91.7 2.7	9.6 0.6	25
	Group						
Pooled	Esmolol	78.3 3.2	144.0 3.8	77.3 2.5	98.8 2.5	11.2 0.6	32
	Placebo	79.7 2.7	139.0 4.6	77.9 2.4	98.2 2.8	11.1 0.6	31
Comparison[b]		N.S.	N.S.	N.S.	N.S.	N.S.	

[a] Significant difference between Centers 3 and 4 (pooled) and Center 6 were detected for HR, SBP, DBP, MAP and RPP ($p<0.05$).
[b] N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).

Ib Analysis by Center of Baseline Parameters

Center Differences: Significant center differences were also found relative to these clinically significant levels of heart rate and systolic blood pressure. A significantly greater proportion (19/38, 50%) of patients in centers 3 and 4 (pooled) had SBP greater than or equal to 180 mm Hg in comparison with center 6 (VA Medical Center, Miami, FL) (5/25, 20%). In addition a significantly greater proportion (26/38, 68%) of patients in centers 3 and 4 (pooled) had HR greater than or equal to 100 bpm or SBP greater than or equal to 180 mm Hg in comparison with center 6 (10/25, 40%).

II Efficacy Results:

Analysis by Treatment Group

The therapeutic responses among "all patients" and "efficacy patients" treated with esmolol and placebo are summarized in Tables 11, 12, 23, 27, 28 and Figures 2 and 3 (HR), 4 and 5 (SBP), 8 and 9 (MAP), and 10 and 11 (RPP). The major therapeutic results were:

(a) Primary Efficacy Variables (Heart Rate and Systolic Blood Pressure:

The esmolol treated group demonstrated a significant (p less than 0.01) blunting of the increase in heart rate and systolic blood pressure when compared to the placebo group (Table 11, 27 and Figure 2-5). Maximum heart rate changes indicated an average increase of 23.9 ± 2.7 bpm for the placebo group as opposed to an average increase of only 7.9 ± 3.0 bpm for the esmolol group (Table 11, 27 and Figures 2 and 3). The maximum systolic blood pressure changes indicated an average increase of 45.5 ± 4.7 mm Hg for the placebo group as opposed to an average increase of only 19.4 ± 4.2 mm Hg for the esmolol group (Table 11, 27 and Figures 4 and 5).

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																		
(bpm)	Esmolol	76.3	3.2	32	68.9	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
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[**]		
(mmHg)	Esmolol	144.8	3.8	32	139.3	3.8	32	129.5	5.0	31	164.2	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
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, * $p<0.05$, ** $p<0.01$

TABLE 27

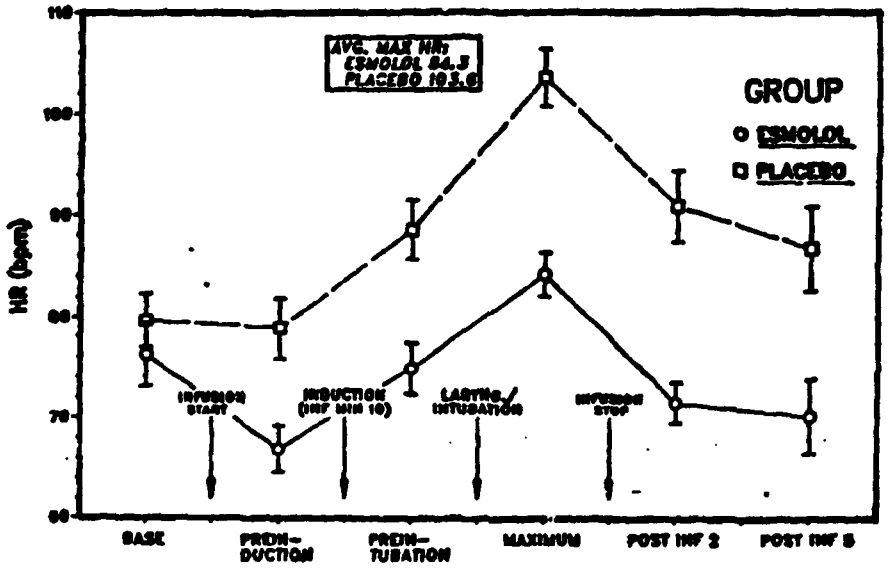
Heart Rate and Systolic Blood Pressure with Changes from Baseline, by Period, for "All Patients" Treated with Esmolol or Placebo

		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 2.5 37	91.5 2.5 37	86.1 2.8 37
HR Change	Esmolol		-9.1# 1.6 36	-0.8 2.2 36	9.0# 2.6 36	-1.8 2.4 36	-4.9 2.8 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 38	-12.7# 4.3 36	-27.9# 4.7 36
	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.
N.S. indicates no significant difference between the esmolol and placebo treatment groups ($p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$

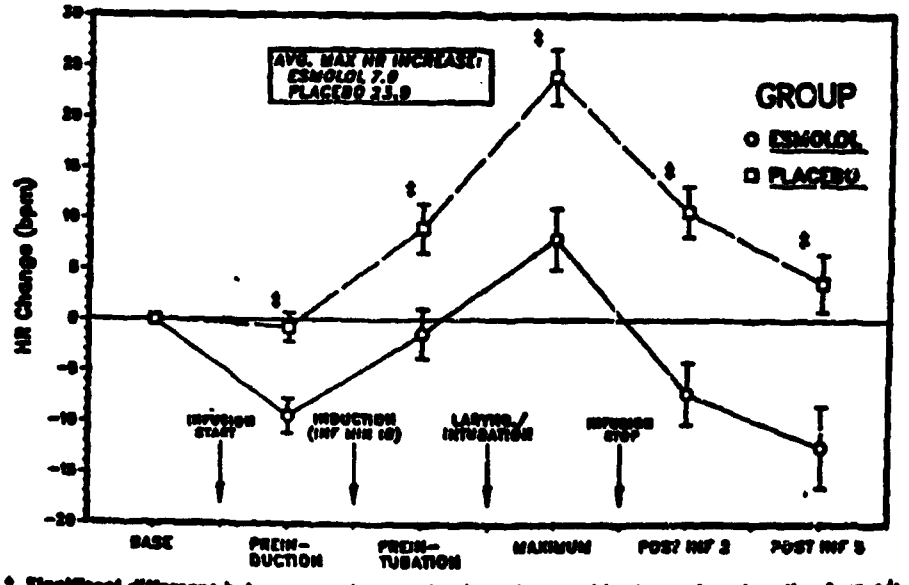
FIGURE 2

Heart Rate
(mean ± standard error)



FIGURE

Heart Rate Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline ($p<0.05$).
‡ $p<0.01$.

FIGURE 4

Systolic Blood Pressure
(mean ± standard error)

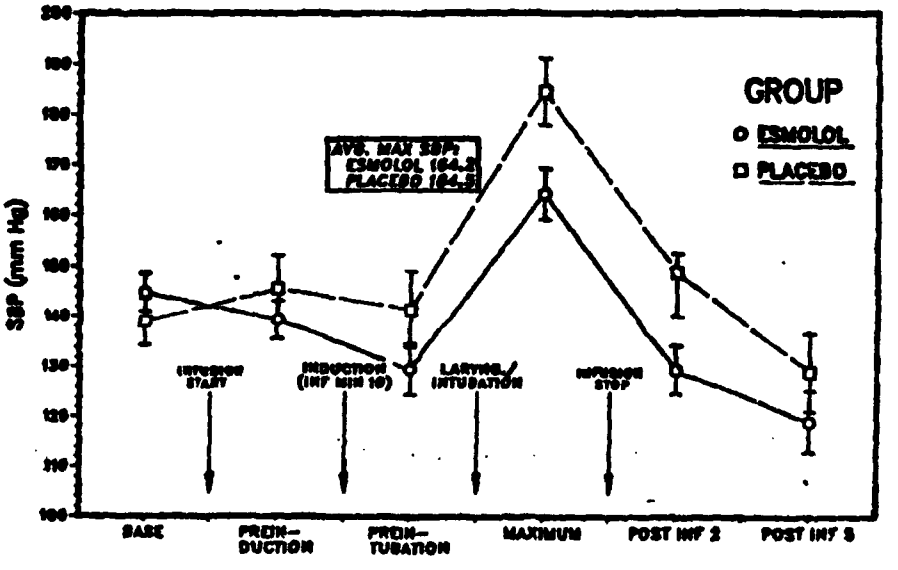
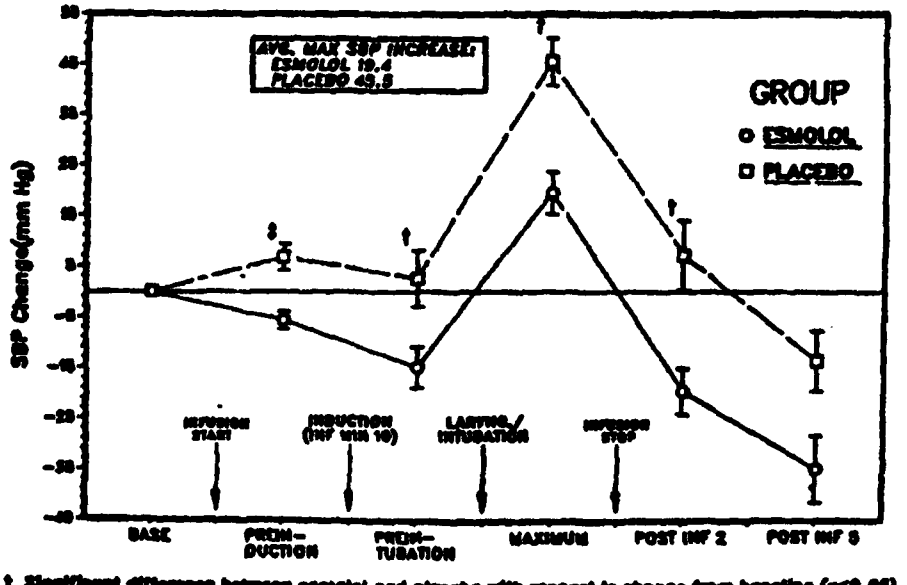


FIGURE 5

Systolic Blood Pressure Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline ($p<0.05$).
‡ $p<0.01$.

(b) Other Efficacy Variables:

Analysis of both mean arterial pressure and rate pressure product revealed similar findings to that of heart rate and systolic blood pressure (both variables exhibited significantly greater increases in the placebo group than in the esmolol group). There was no significant difference between the two study groups for diastolic blood pressure with respect to maximum changes from baseline.

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	76.3	2.3	32	81.3	3.9	31	108.8	3.7	32	79.9	3.7	24	71.7	4.8	15
	Placebo	77.8	2.4	31	77.3	2.7	31	81.7	3.8	31	108.8	3.2	31	84.8	3.2	25	75.2	4.0	19
DBP Change	Esmolol				-1.1	1.8	32	4.4	3.7	31	26.5	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	4.0	31	124.7	3.9	32	98.1	4.0	24	87.8	5.0	15
	Placebo	98.2	2.8	31	100.1	3.6	31	101.6	4.9	31	133.1	3.7	31	108.9	4.7	25	93.1	6.1	19
MAP Change	Esmolol				-2.5	1.6	32	-2.0	3.8	31	24.8	3.5	32	-8.0[d]	3.7	24	-18.4[d]	5.2	15
	Placebo				1.9	1.3	31	3.4	3.7	31	34.9	3.0	31	9.3	3.6	25	-9.1[d]	4.8	19
Comparison of Change[b]		N.S.			P>E*			N.S.			P>E*			P>E*			N.S.		
RPP	Esmolol	11.2	0.6	32	9.4	0.4	32	9.9	0.6	31	13.3	0.6	32	9.3	0.6	24	8.4	0.7	15
	Placebo	11.1	0.6	31	11.7	0.9	31	12.8	1.0	31	18.3	0.9	31	13.8	1.1	25	11.3	0.9	19
RPP Change	Esmolol				-1.8[d]	0.3	32	-1.4[d]	0.6	31	2.1	0.7	32	-2.4[d]	0.7	24	-4.2[d]	1.1	15
	Placebo				0.6	0.4	31	1.7[d]	0.8	31	7.2	0.8	31	2.3[d]	0.8	25	-0.6	0.7	19
Comparison of Change[b]		N.S.			P>E**			P>E**			P>E**			P>E**			P>E*		

[d] 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 #429.
[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

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 38	82.2 3.0 35	106.3 3.4 36	81.0 3.4 36	71.4 3.0 36
	Placebo	77.9 2.3 37	77.3 2.8 37	83.0 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 38	4.8 3.7 35	28.5[c] 3.1 36	3.2 3.2 36	-6.5[c] 3.1 36
	Placebo		-0.7 1.1 37	5.8[c] 2.8 37	31.8[c] 2.4 37	5.0[c] 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	98.8 2.3 36	97.1 2.4 36	99.2 4.1 35	134.9 3.8 36	97.7 3.8 36	88.2 3.3 36
	Placebo	98.1 2.8 37	99.5 3.3 37	103.5 4.3 37	133.3 3.4 37	102.7 3.7 37	89.5 3.8 37
MAP Change	Esmolol		-2.7 1.4 36	-1.2 3.7 35	25.1[c] 3.2 36	-2.1 3.4 36	-13.8[c] 3.5 36
	Placebo		1.4 1.2 37	5.4 3.3 37	35.2[c] 2.7 37	4.6 2.7 37	-8.6[c] 2.9 37
Comparison of Change[b]		N.S.	P>E[c]	N.S.	P>E[c]	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 0.8 36	8.3 0.4 36
	Placebo	11.0 0.5 37	11.5 0.7 37	13.0 0.9 37	18.1 0.9 32	13.2 0.8 37	10.6 0.6 37
RPP Change	Esmolol		-1.8[c] 0.3 36	-1.2[c] 0.6 35	2.3[c] 0.6 36	-1.3[c] 0.6 36	-2.7[c] 0.6 36
	Placebo		0.5 0.4 37	2.1[c] 0.7 37	7.1[c] 0.8 37	2.2[c] 0.8 37	-0.3 0.6 37
Comparison of Change[b]		N.S.	P>E[cc]	P>E[cc]	P>E[cc]	P>E[cc]	P>E[cc]

a 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 #475.
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, [c] $p<0.05$, [cc] $p<0.01$

(c) Clinically Significant Increases in HR and SBP: (Table 15)

There was a significantly greater number of patients who demonstrated HR greater or equal to 100 bpm in the placebo group (18/31, 58%), than in the esmolol treated group (4/32, 13%, p less than 0.01). In addition there was a significantly greater number of placebo patients (23/31, 74%) that demonstrated either a HR greater than or equal to 100 bpm or a SBP greater than or equal to 180 mm Hg as compared to the esmolol group (13/32, 41%, p less than 0.01); and a significantly greater number of placebo patients (8/31, 26%) that demonstrated a HR greater than or equal to 100 and a SBP greater than or equal to 180 as compared to the esmolol group (2/32, 6%, p less than 0.05).

TABLE 15

Clinically Significant Heart Rate (bpm) and Systolic Blood Pressure (mm Hg)

		HR≥100	SBP≥180	HR≥100 AND SBP≥180	HR≥100 OR SBP≥180	N
Center[a]	Group					
3 & 4	Esmolol	4	10	2	12	19
	Placebo	11	9	6	14	19
8	Esmolol	0	1	0	1	13
	Placebo	7	4	2	9	12
	Group					
Pooled	Esmolol	4	11	2	13	32
	Placebo	18	13	8	23	31
	Comparison[b]	P>E**	N.S.	P>E*	P>E**	

a Centers 3 and 4 (pooled) had a significantly greater proportion of patients with SBP ≥180 (mm Hg) and a greater proportion of patients with SBP ≥180 (mm Hg) or HR ≥100 (bpm) than Center 8.

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. * $p<0.05$, ** $p<0.01$

(d) Analysis of Maximum Changes from Baseline by Center

In addition to pooling the data from the various centers for the above primary efficacy analysis, the response rates observed at the various centers were compared (Center 3 and 4 were pooled). For HR, SBP, RPP statistical significance was attained in both the centers. With respect to comparisons between the two treatment groups, esmolol significantly blunted the increase in HR, SBP and RPP (Table 23).

Table 23

Maximum Change from Baseline for "Efficacy Patients" by Center and Treatment

		HR Change (bpm)	SBP Change (mm Hg)	DBP Change (mm Hg)	MAP Change (mm Hg)	RPP Change	
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	N
Center	Group						
3 & 4	Esmolol	9.2* 3.8	22.3** 4.4	32.3 4.0	28.1 3.7	3.7** 0.9	19
	Placebo	20.2* 3.6	51.1** 8.6	29.5 3.8	35.8 3.9	7.2** 0.9	19
8	Esmolol	6.1** 5.2	15.0 8.2	22.9 5.7	20.1 6.6	1.3** 1.2	13
	Placebo	28.6** 3.0	38.8* 5.4	32.7 4.5	33.8 4.7	7.2** 0.8	12

* Indicates significant difference between the esmolol and placebo treatment groups ($p<0.05$).
** Indicates significant difference between the esmolol and placebo treatment groups ($p<0.01$).

(e) Analysis of Changes in "All Patients": Analysis revealed that results were similar to those seen with the "efficacy patients", with the exception of diastolic and mean arterial blood pressure changes at the post infusion periods. For example, maximum heart rate, systolic and mean arterial blood pressures, and rate pressure product increases were all significantly blunted following intubation in the esmolol treated patients.

III Safety Results

a) Adverse Effects:

Safety was assessed in all the patients entering the study: esmolol (n=36), and placebo (n=37). No adverse effects were reporting during the study.

b) Other Noted Effects:

One patient (#631) who received esmolol developed hypotension (72/45 mmHg). This patient developed hypotension 5 minutes post infusion, which continued to fall (71/38 mmHg) one minute later at which time the patient received ephedrine (5 mg IV) (6 minutes after discontinuing the study drug infusion). Four minutes after the ephedrine was administered the pressure was noted to be 91/52 mmHg. The investigator attributed the hypotension to the inhaltion agent (halothane, 4% inspired). However, this raises the issue of what the actual incidence of post infusion hypotension was in the "all patient" cohort and not the selected cohort (esmolol n=15, placebo n=19) reported by the sponsor. According to the trend evident in Table 11, SBP at the 10 and 15 minute post infusion period would project further significant decreases in SBP. As previously pointed out, there are number of errors in the calculation of the mean changes in HR, SBP, DBP, MAP and RPP during the post infusion periods (Tables 11 and 12).

c) Deaths:

None were reported.

Reviewer's Note

Thus there are two problems with respect to evaluating the safety data (clinical safety variables) observed in this trial: (a) arbitrary partial exclusion of efficacy variables in 50/63 patients during the course of the study period (especially the post infusion period where one would anticipate rapid recovery from esmolol) and (b) computational errors in the data tables. These latter two concerns have been communicated to the sponsor.

IV Review of Pivotal Studies

B. Perioperative Tachycardia and Hypertension

Study No. 8052-84-49 (Third Pivotal Study)

Overview

This is the third randomized parallel placebo controlled multicenter trial conducted by the sponsor to establish the efficacy and safety of esmolol in attenuating perioperative tachycardia and hypertension associated with endotracheal intubation. Again, the study objectives, design, treatment plan and therapeutic endpoints (primary and secondary efficacy variables) are practically identical to the two previous trials (i.e., 51A and 51B). The only significant differences relate to the (a) target study patient population (in this case only patients undergoing carotid artery endarterectomy or external catroid to internal carotid by-pass surgery) and (b) the maintenance general anesthesia (isoflurane [0-6% inspired]). The dose and duration of esmolol infusion was identical to study 51A. Specific results of this study will be presented below. However, some overall impressions will be made here. In general the overall therapeutic results in terms of the primary and secondary efficacy variables were similar to the two previously reported trials (51A and 51B). Esmolol was found to be effective in blunting the increases in HR, SBP, DBP, MAP and RPP following endotracheal intubation. Interestingly, the positive effect in this trial on DBP was not seen in the other two trials. Esmolol also prevented clinically significant increases in HR (greater than or equal to 100 bpm) and SBP (greater than 180 mmHg) following intubation compared to placebo. Similar to the two previous trials, the sponsor has decided to partially exclude the analysis of efficacy data from a majority of the "efficacy patients" (55/62) for what the sponsor describes as "medical interventions that confounded the interpretation of the efficacy data". In this case, 44 patients had partial exclusion of data because of changes in the inspired dose of isoflurane. Another 11 patients had exclusion of data because of pancuronium (5 patients) and supplemental thiopental (6 patients). Again this partial exclusion of efficacy data precludes our ability to analyze the changes in efficacy variables between the two treatment groups during the post infusion study points (2 minutes and 5 minutes post infusion). Another problem encountered in this study (also occurring in 51B) are a number of mistakes in the calculation of data points for HR and SBP in Table 11. In addition, another potential problem is the difference in the mean baseline values of the primary efficacy variables for the "efficacy patients" in the two treatment groups (HR: esmolol 74.4 vs 80.0; SBP: esmolol 184.3 vs 168.7). The impact of these differences is not clear and according to the sponsor's calculations these differences are not statistically significant. It is also worth noting that the effect of esmolol in blunting the maximum increase in HR and SBP was much more pronounced in study 49 than in 51A and 51B. This data is summarized below.

Study		Baseline (mean) HR (bpm)	SBP (mm Hg)		Maximum (mean) HR	SBP
#49	BREV	74.4	184.3	B	82.3	185.8
	PBO	80	168.7	P	104	214.1
#51A	B	73.9	131.8	B	97.1	157.9
	P	74.7	128.5	P	112.3	168.7
#51B	B	76.3	144.8	B	84.3	164.2
	P	79.7	139	P	103.6	184.5

There are several possible explanations for the decreased maximum response observed in patients enrolled in study 49 including 1) target population is more inherently sensitive to esmolol (the relative dose per patient is greater), 2) target population has less adrenergic reserve and/or response and 3) other hemodynamic confounding variables, i.e., isoflurane, increased thiopental, etc. The latter two explanations are unlikely since the placebo group in study 49 had a good response in HR and SBP: and placebo patients received the same dose of isoflurane and thiopental. However there could be an enhanced effect due to the interaction of esmolol and a relatively larger dose of thiopental (6 mg/kg). Nevertheless, the first explanation cannot be excluded and it is quite possible that these patients with carotid artery disease (CAD) are more intrinsically sensitive to esmolol. Pharmacodynamic data from the Clinical Pharmacology review suggests that some patients with CAD have less cardiac reserve (↓CI) than normal subjects and are thus more sensitive to the negative inotropic effect of beta blockers. This hypothesis is relevant because of the cardiovascular side effects noted with esmolol in study 49. Although the incidence of hypotension seems similar in both treatment groups (five in each), at least two patients (probably four patients) treated with esmolol developed ST-segment changes indicative of myocardial ischemia (see discussion under adverse effects). Since prevention or reduction in the risk of myocardial ischemia is one of the proposed advantages of esmolol (see Background/Rationale) this is suggestive evidence that in certain patients, esmolol may produce the very response it is suppose to prevent. Since the number of cases is small and the data from the post infusion period is incomplete, the mechanism of these ischemic changes is not entirely clear (i.e., myocardial depression, decrease in systemic vascular resistance and/or hypoperfusion).

B. Specific Results

For details of the study objectives, design, treatment plan and efficacy and safety assessment (see description under study 51A).

C. Investigators and Institutes

Six of the 7 investigators who participated in this study were board certified anesthesiologists and the remaining investigator was a board certified cardiologist (Dee Wood). Of the 7 centers selected to participate in this study, 5 centers enrolled 4 or more patients. The other two centers (Center 3: University Hosptial, London, Ontario and the original center 4: Brigham and Woman's Hospital, Boston) obtained IRB approval but did not enter any patients. For a complete listing of the investigators, institutions, and the number of patients enrolled at each center, see Table 1.

Table 1

LIST OF INVESTIGATORS AND NUMBER OF PATIENTS ENROLLED

Center Number	Investigator and Institution	Number of Patients Enrolled
1	Maurice S. Albin, M.D.,M.Sc. University of Texas Health Science Center at San Antonio San Antonio, Texas	4
2	Roy F. Cucchiara, M.D. Mayo Clinic Rochester, Minnesota	20
3	Adrian Gelb, M.D. University Hospital London, Ontario Canada	0
4	Stanley Lee Son, M.D. Brigham and Women's Hospital Boston, Massachusetts	0 (Replaced by Dr. DeWood)
4	Marcus DeWood, M.D. Sacred Heart Hospital Spokane, Washington	12
5	Richard S. Matteo, M.D. Neurological Institute New York, New York	14
6	Michael Roizen, M.D. University of California San Francisco, California	24

Study Design: The design of this study was double-blind, randomized, parallel, and placebo controlled. All patients received an intravenous infusion of either esmolol (300 mcg/kg/min) or placebo which was started five minutes prior to induction of anesthesia and continued during and for 7 minutes after induction for a total infusion time of 12 minutes.

Patient Selection: Patients were selected for this study according to the following entrance criteria:

(a) Inclusion Criteria: Either males or nonpregnant females, (as confirmed by a negative pregnancy test just prior to entry in the study in those females of childbearing potential) who were candidates for carotid endarterectomy or external carotid to internal carotid bypass surgery.

(b) Exclusion Criteria: See study 51A.

Number of Patients: "All", "efficacy", "dropouts" and "exclusions." 74 patients were entered into this multicenter study and were randomized to either esmolol or placebo. These were referred to as "all patients." Of these 74 "all patients", 62 were classified as "efficacy patients" (n=32 for esmolol and n=30 for placebo). For the derivation of "all patients" and "efficacy patients" in the study see Table 5.

Table 5

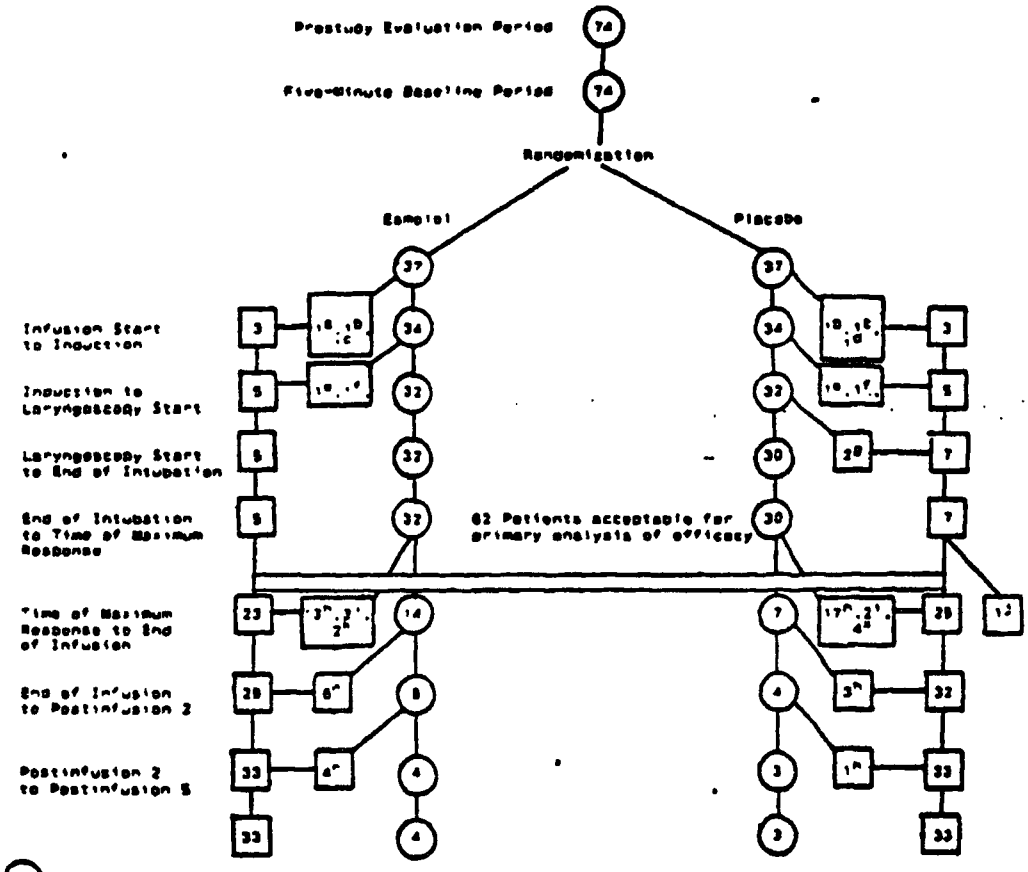
DERIVATION OF "ALL PATIENTS" AND "EFFICACY PATIENTS" IN THE STUDY

"All Patients"	74		37 Esmolol 37 Placebo
Excluded from Efficacy Analysis	12	(#602, 603, 606, 613, 619) Esmolol (#225, 407, 512, 604, 605, 607, 623) Placebo	
"Efficacy Patients"	62		32 Esmolol 30 Placebo

For a summary of "all patients" at each phase of the study see Table 6.

TABLE 6

SUMMARY OF "ALL PATIENTS" AT EACH PHASE OF THE STUDY



Eligible for efficacy analysis

Ineligible for efficacy analysis; outside columns indicate cumulative total excluding patients who did not complete study.

a 12-minute 500 mcg/kg/min infusion (Patient 602)
b 2-min loading dose--200 mcg/kg/min infusion (Patients 603, 604)
c Patient on reserpine (Patients 407, 613)
d Repeat patient (Patient 605)
e Intraprocedural titrating administration (Patients 606, 607)
f Thiopental dose >12 mg/kg (Patients 619, 623)
g Multiple intubations (Patients 225, 512)
h Isoflurane change (% inspired: See Appendix I for patient numbers.
i Pancuronium administration (Patients 206, 214, 221, 230, 235)
j Patient 607 previously excluded for intraprocedural titrating; infusion terminated at minute 8.5
k Thiopental readministered (Patients 201, 403, 405, 406, 609, 620)

For a list of the patients excluded from the efficacy analysis see Table 7.

Table 7

LIST OF PATIENTS EXCLUDED FROM EFFICACY ANALYSIS

Patient Number	Treatment	Demographic Data			Baseline Data			Reason for Exclusion from Efficacy Analysis
		Sex	Age (yrs)	Weight (kg)	Heart Rate (bpm)	Blood Pressure SBP (mm Hg)	DBP	
220	Placebo	M	53	80	86	182	87	Multiple intubations
407	Placebo	M	58	77	78	190	78	Patient was receiving reserpine.
512	Placebo	M	73	81	68	181	85	Multiple intubations
602	Esmolol	F	59	60	77	151	69	Patient received an incorrect maintenance infusion dosage (500 mcg/kg/min instead of 300 mcg/kg/min).
603	Esmolol	M	82	62	80	180	68	Patient was administered a 200 mcg/kg/min maintenance infusion. Although this was correct at the time, the protocol was later amended back to 300 mcg/kg/min. Therefore, these data could not be used.
604	Placebo	F	71	63	65	179	93	Patient was administered a 200 mcg/kg/min maintenance infusion. Although this was correct at the time, the protocol was later amended back to 300 mcg/kg/min. Therefore, these data could not be used.
605	Placebo	F	71	61	68	156	65	This patient was studied on two separate occasions (this represents the second study entry).
606	Esmolol	M	51	72	103	143	78	Intratracheal lidocaine administered prior to intubation.
607	Placebo	M	83	67	84	188	101	Intratracheal lidocaine administered prior to intubation.
613	Esmolol	M	79	81	53	178	69	Patient was receiving reserpine.
619	Esmolol	M	51	87	54	182	75	Received a 12.3 mg/kg dosage of thiopental within a five minute period.*
623	Placebo	M	52	75	73	173	85	Received a 13.7 mg/kg dosage of thiopental within a five minute period.*

* Acceptable upper limit of 12 mg/kg within 5 minutes.

Interestingly, 3 of the patients excluded (#602, 613, 619) developed ischemia during the esmolol infusion.

As can be seen from Table 7, 12 "all patients" were not included in the "efficacy patients" group for the following reasons: received unacceptable prior or concurrent medications (4 patients), incorrect esmolol dosage (3 patients), difficult intubation requiring several attempts (2 patients), deviations from dose allowed for anesthesia induction (2 patients), and 1 patient was studied on 2 separate occasions. Hence, of the 12 exclusions - 7 were from the placebo group and 5 were from the esmolol group. Analysis of the effect of esmolol and placebo on heart rate and blood pressure and other efficacy variables was performed on 62 "efficacy patients" as well as on "all patients".

Efficacy and Safety Data: Safety was based on the data from all 74 patients. In addition, as previously noted in the overview section, the sponsor arbitrarily excluded part of the efficacy data on a number of "efficacy patients" because of changes in the inspired dose of isoflurane during the course of the study. A total of 44 patients were thus affected. Other patients had partial efficacy data excluded because other interventions (according to the sponsor) similarly produced confounding hemodynamic effects. These included: pancuronium administered, 5 patients; and supplemental thiopental administered after laryngoscopy, 6 patients. Thus in all, 55 of the 62 "efficacy patients" had partial heart rate and blood pressure data excluded subsequent to medical interventions.

Study Results:

I. Baseline Demographics and Comparability of Treatment Groups

Baseline demographics and clinical characteristics (including key efficacy variables) are provided in Tables 8B, 9, 10 and 13.

Table 8B

SUMMARY OF DEMOGRAPHIC DATA BY CENTER*,
EFFICACY ELIGIBLE, EFFICACY INELIGIBLE AND "ALL PATIENTS"

	ASA PHYSICAL STATUS			SEX		RACE			
GROUP	II	III	IV	M	F	CAUC	BLACK	ORNTL	OTHER
Center 1 & 4	7	9	0	13	3	16	0	0	0
Center 2	3	17	0	13	7	20	0	0	0
Center 5	13	1	0	10	4	14	0	0	0
Center 6	5	16	2	14	9	20	0	1	2
Eligible+	26	34	2	41	21	60	0	1	1
Ineligible++	2	9[a]	0	9	2[a]	10[a]	0	0	1
"All Patients"	28	43	2	50	23	70	0	1	2

* Center 3 did not enter any patients.
++ Indicates significant difference among the centers ($p<0.05$).
\+ Patients eligible for efficacy analysis.
++ Patients ineligible for efficacy analysis.
[a] Patient #605 was omitted from this table since this patient and Patient #604 (also ineligible) were the same person.

Note: For all variables, the distribution by eligibility for efficacy analysis were not significantly different ($p\geq0.05$).

Table 9

SUMMARY OF PRESTUDY CLINICAL DATA BY CENTER,* EFFICACY ELIGIBLE, EFFICACY INELIGIBLE AND "ALL PATIENTS"

VARIABLE	GROUP	N	MEAN ± S.D.	RANGE
HEART RATE (bpm)	Center 1 & 4	16	73.1 ± 13.9	50 - 104
	Center 2	20	73.6 ± 13.7	51 - 98
	Center 5	14	70.6 ± 11.1	51 - 92
	Center 6	23	78.2 ± 13.1	53 - 102
	Eligible+	62	73.4 ± 13.1	50 - 104
	Ineligible++	11**	79.8 ± 12.6	53 - 102
	"All Patients"	73	74.3 ± 13.1	50 - 104
SYSTOLIC BLOOD PRESSURE*** (mm Hg)	Center 1 & 4	16	149.3 ± 17.6	114 - 180
	Center 2	20	145.1 ± 16.1	110 - 190
	Center 5	14	129.4 ± 17.4	106 - 160
	Center 6	23	141.7 ± 15.4	110 - 170
	Eligible+	62	141.4 ± 17.5	106 - 190
	Ineligible++	11**	144.8 ± 17.9	120 - 180
	"All Patients"	73	141.9 ± 17.5	106 - 190
DIASTOLIC BLOOD PRESSURE (mm Hg)	Center 1 & 4	16	79.2 ± 10.9	60 - 95
	Center 2	20	80.1 ± 9.8	55 - 94
	Center 5	14	78.0 ± 6.4	70 - 90
	Center 6	23	78.5 ± 6.2	60 - 90
	Eligible+	62	78.7 ± 8.9	55 - 95
	Ineligible++	11**	80.7 ± 4.4	74 - 90
	"All Patients"	73	79.0 ± 8.4	55 - 95

* Center 3 did not enter any patients.
** Patient #605 was omitted from this table since this patient and patient #604 (also ineligible) were the same person.
*** Indicates significant difference among the centers ($p < 0.05$)
\+ Patients eligible for efficacy analysis.
++ Patients ineligible for efficacy analysis.
Note: For all variables, mean values for eligible and ineligible were not significantly different ($p \geq 0.05$).

Table 10

Summary of Demographic and Prestudy Clinical Data, by Treatment Group for "All Patients"

Variable	Treatment[a]	Mean ± S.D.		Min	Max	N
Age (years)	Esmolol	65.8	9.1	51.0	82.0	37
	Placebo	65.1	9.4	47.0	83.0	38[c]
Height (cm)[b]	Esmolol	169.2	9.4	154.9	185.0	37
	Placebo	168.9	10.4	150.0	191.0	35[c]
Weight (kg)	Esmolol	72.9	11.6	50.0	96.0	37
	Placebo	72.3	13.2	50.0	105.0	38[c]
BSA (m^2)[b]	Esmolol	1.8	0.2	1.5	2.2	37
	Placebo	1.8	0.2	1.4	2.3	35[c]
Heart Rate (bpm)	Esmolol	74.0	13.6	50.0	102.0	37
	Placebo	74.7	12.8	51.0	104.0	38[c]
SBP (mm Hg)	Esmolol	141.5	15.9	110.0	170.0	37
	Placebo	142.4	19.2	106.0	190.0	38[c]
DBP (mm Hg)	Esmolol	79.2	8.3	60.0	94.0	37
	Placebo	78.8	8.3	55.0	95.0	38[c]

[a] Patient #805 was omitted from this table since this patient and Patient #804 (also ineligible) were the same person.
[b] Height and body surface area were not obtained from Patient #214.
[c] No significant differences between the esmolol and placebo treatment groups were detected ($p \geq 0.05$).

Table 13

Summary of Baseline Observations for "Efficacy Patients", by Center and Treatment Group

		HR, bpm		SBP, mm Hg		DBP, mm Hg		MAP, mm Hg		RPP		
		Mean ± SEM		Mean ± SEM		Mean ± SEM		Mean ± SEM		Mean ± SEM		N
Center[a]	Group											
1 & 4	Esmolol	74.0	5.3	183.5	6.9	77.2	4.3	116.0	4.5	14.7	1.5	5
	Placebo	84.1	8.7	183.8	14.5	89.2	6.2	116.8	8.5	15.1	1.3	6
	Pooled	78.4	4.7	180.6	6.9	79.6	3.5	118.3	4.1	14.8	1.0	15
2	Esmolol	70.6	4.0	191.8	8.4	86.7	4.6	121.8	4.8	13.6	0.8	9
	Placebo	76.9	4.8	198.7	8.7	78.2	2.7	98.7	4.3	12.2	1.0	10
	Pooled	73.9	3.1	174.4	7.1	78.0	3.2	110.1	4.0	12.8	0.7	19
5	Esmolol	70.4	8.4	183.9	11.4	73.1	7.1	103.4	8.4	11.8	1.3	8
	Placebo	77.8	4.8	159.4	8.8	78.2	5.1	100.0	5.5	12.5	1.2	7
	Pooled	74.4	3.6	161.5	6.7	71.8	4.1	101.5	4.7	12.1	0.9	13
6	Esmolol	81.4	3.5	180.7	10.7	76.2	4.7	111.1	3.5	14.7	1.0	8
	Placebo	82.9	3.3	179.2	7.7	73.8	3.9	108.9	3.8	15.0	1.1	7
	Pooled	82.1	2.3	180.0	6.5	75.1	3.0	110.1	3.3	14.8	0.7	15
	Group											
Pooled	Esmolol	74.4	2.3	184.5	4.0	78.8	2.5	114.0	2.9	13.8	0.6	32
	Placebo	80.0	2.6	188.7	4.1	73.7	2.2	105.3	2.8	13.5	0.6	30
Comparison[b]		N.S.		N.S.		N.S.		N.S.		N.S.		

[a] No significant difference among the centers was detected for [illegible]
[b] N.S. indicates [illegible]

There were no significant differences among the key clinical characteristics between the two treatment groups. The patients ranged in age from 47 to 83 years with a mean of 66 years. Forty (55%) patients were 65 years of age or older. Fifty (68%) patients were male and 23 (32%) were female. The majority (96%) of the patients were caucausians. There were 28 (38%) patients classified ASA physical status II, 43 (59%) as ASA physical status III and 2 (3%) patients were classified as physical status IV by the investigators.

II Efficacy Results

1) Analysis by Treatment Group

The overall therapeutic results of esmolol compared to placebo are summarized in Tables 11, 12, 14, 15, 22, 27 and Figures 2-11. The specific results for the key efficacy variables are as follows:

(a) Primary efficacy variables (see Figures 2-5) as summarized by the sponsor "esmolol significantly blunted the increases in heart rate and blood pressure when compared to placebo (p less than 0.01). The average maximum heart rate increase in placebo treated patients was 24 bpm as compared to an average increase of 8 bpm in patients treated with esmolol. The average maximum systolic blood pressure increase in the placebo group was 45 mmHg, while an average increase of 1.5 mmHg was observed in the esmolol group (Table 11).

FIGURE 2

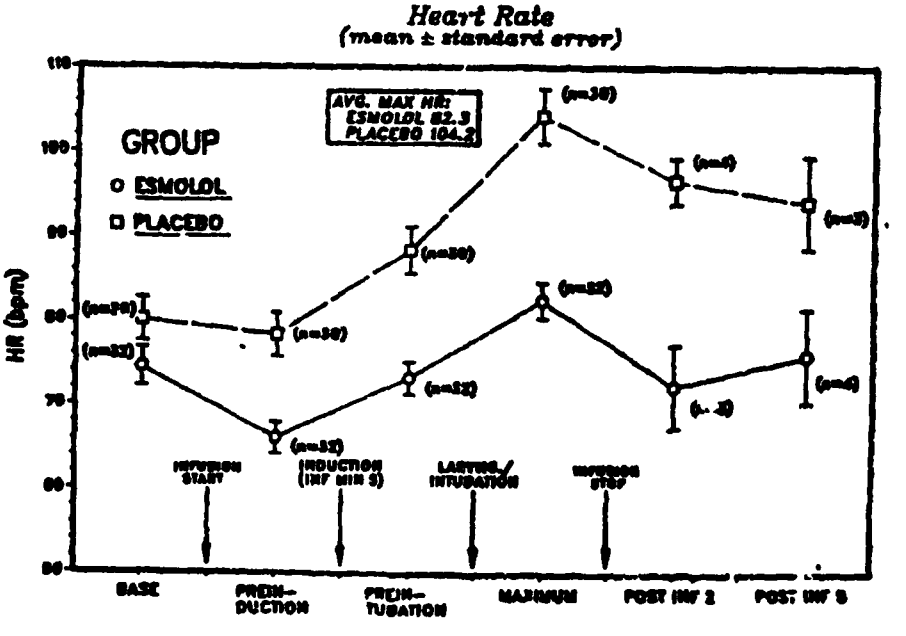
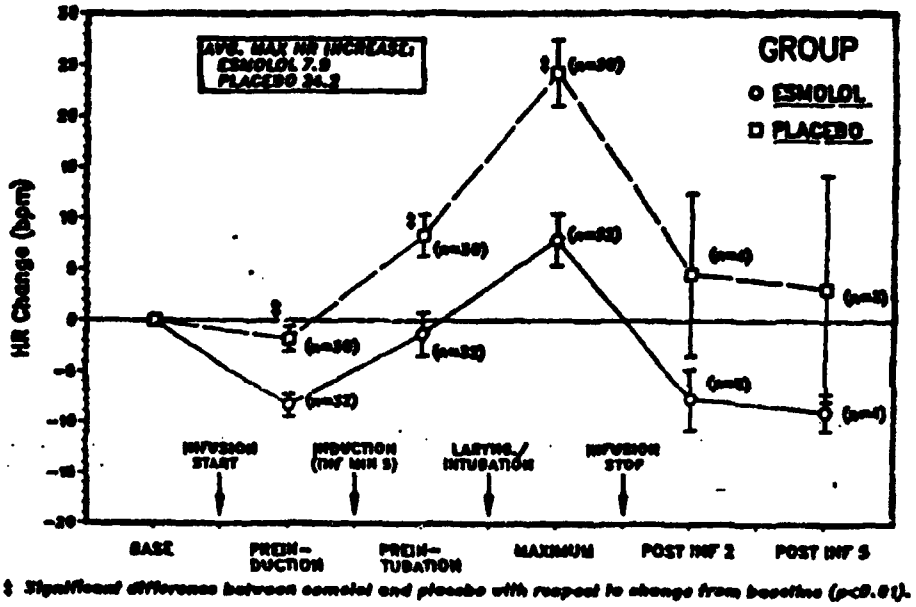


FIGURE 3

Heart Rate Changes from Baseline
(mean ± standard error)



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

FIGURE 4

Systolic Blood Pressure
(mean ± standard error)

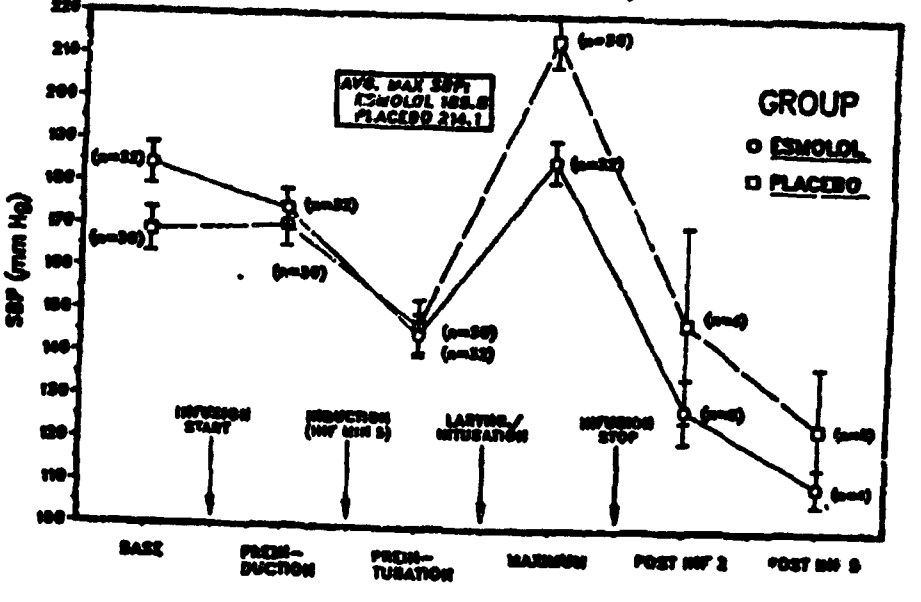
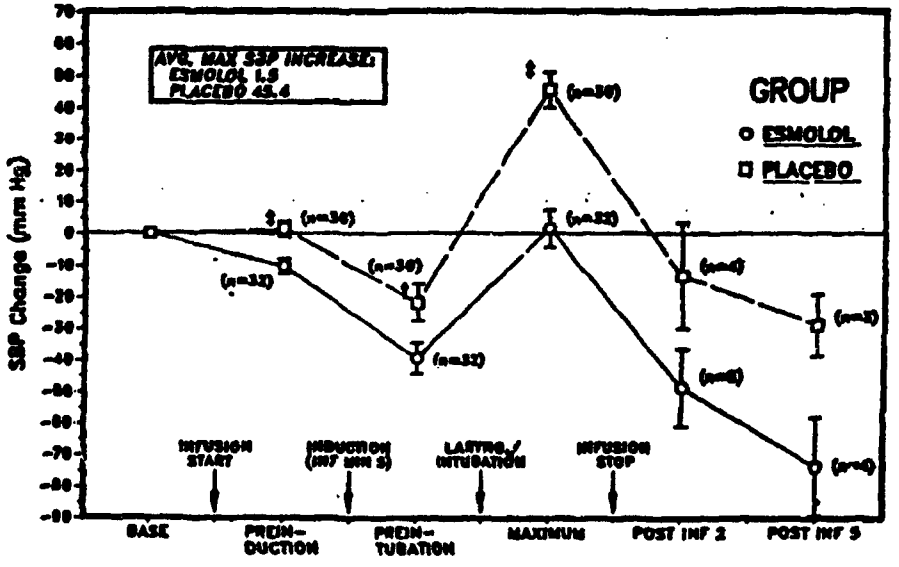


FIGURE 9

Systolic Blood Pressure Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline ($p<0.05$).
‡ $p<0.01$.

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	2.6	30	78.2	2.6	30	88.3	2.8	30	104.2	3.2	30	96.5	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*	1.6	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[@]		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	144.6	5.0	32	185.8	4.9	32	127.9	7.5	8	110.5	4.4	4
	Placebo	188.7	5.1	30	170.1	4.9	30	146.8	6.1	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*	4.9	32	1.5	5.9	32	-48.7*	12.3	8	-73.7*	15.5	4
	Placebo				1.4	2.6	30	-21.9*	5.8	30	45.4	5.5	30	-13.3	16.8	4	-28.8	9.7	3
Comparison of Change[@]		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.
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, $p\geq0.05$).
P = Placebo, E = Esmolol 300 mcg/kg/min, * $p<0.05$, ** $p<0.01$.

(b) Secondary efficacy variables (DBP, MAP, RPP). Analysis of DBP (Figures 6 and 7), MAP (Figures 8 and 9) and RPP (Figures 10 and 11) revealed similar findings to that of HR and SBP. All three variables exhibited significantly greater increases in the placebo group than in the esmolol group. Rate pressure product in the placebo treated group increased from 14 bpm . mm Hg X 1000 at baseline to a maximum of 22 bpm . mm Hg X 1000 while in the esmolol treated group this increase was markedly blunted (14 bpm . mm Hg X 1000 at baseline to a maximum of 15 bpm . mm Hg X 1000).

FIGURE 6

Diastolic Blood Pressure
(mean ± standard error)

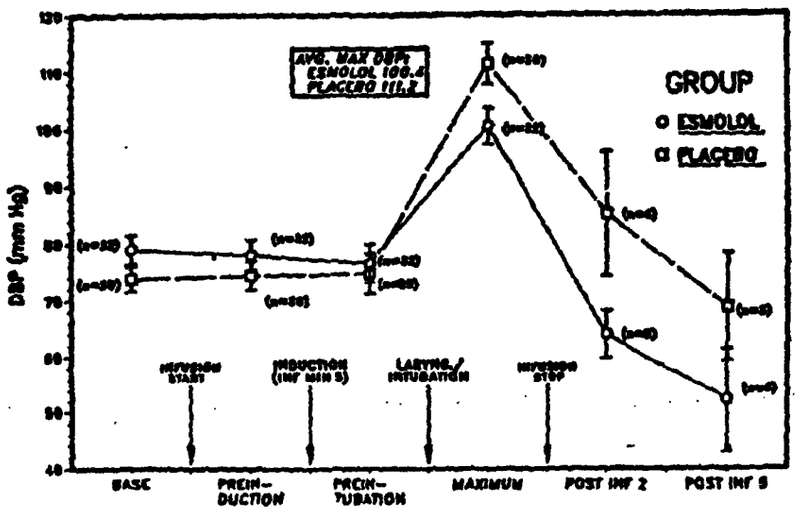
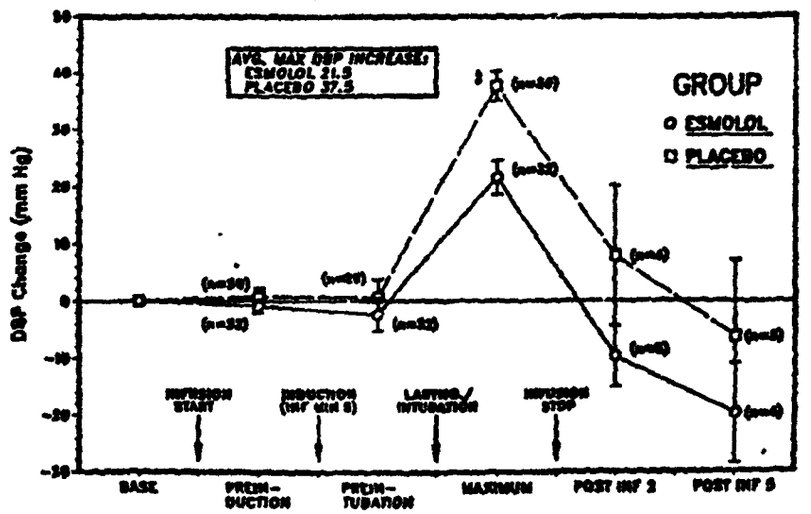


FIGURE 7

Diastolic Blood Pressure Changes from Baseline
(mean ± standard error)



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

FIGURE 8

Mean Arterial Blood Pressure
(mean ± standard error)

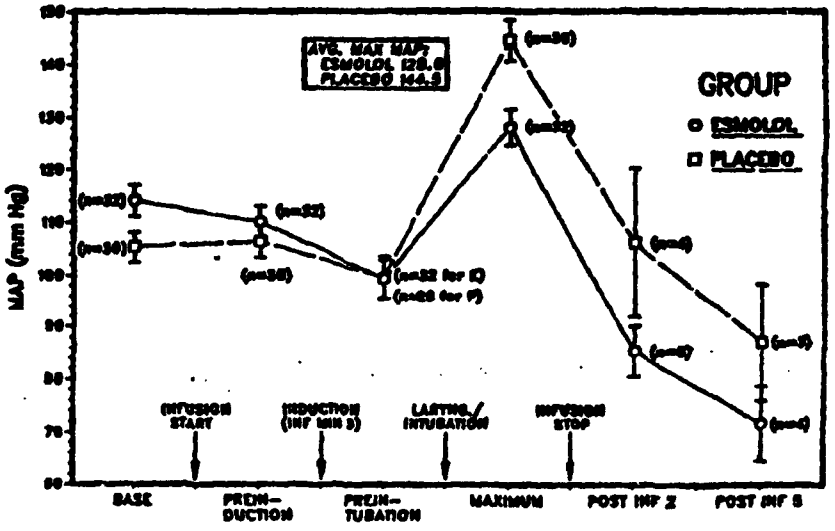
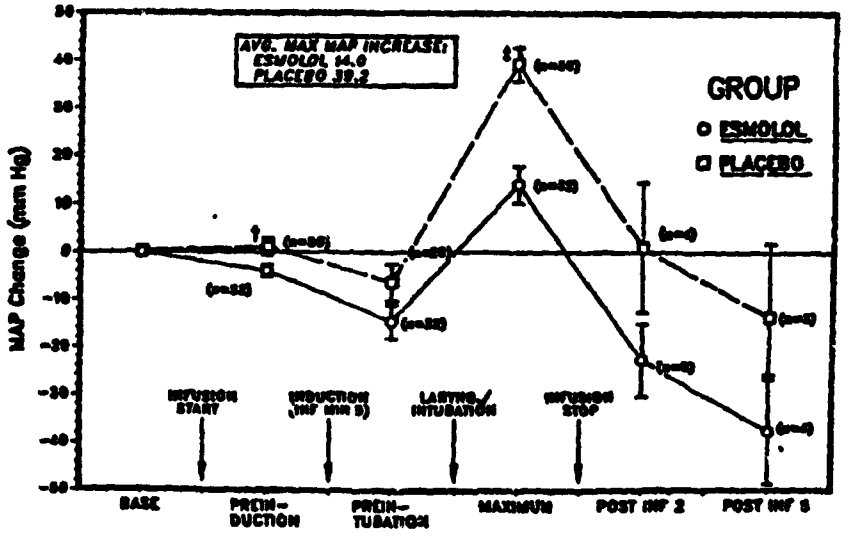


FIGURE 9

Mean Arterial Pressure Changes from Baseline
(mean ± standard error)



† Significant difference between esmolol and placebo with respect to change from baseline ($p<0.05$).
‡ ($p<0.01$).

FIGURE 10

Rate–Pressure Product
(mean ± standard error)

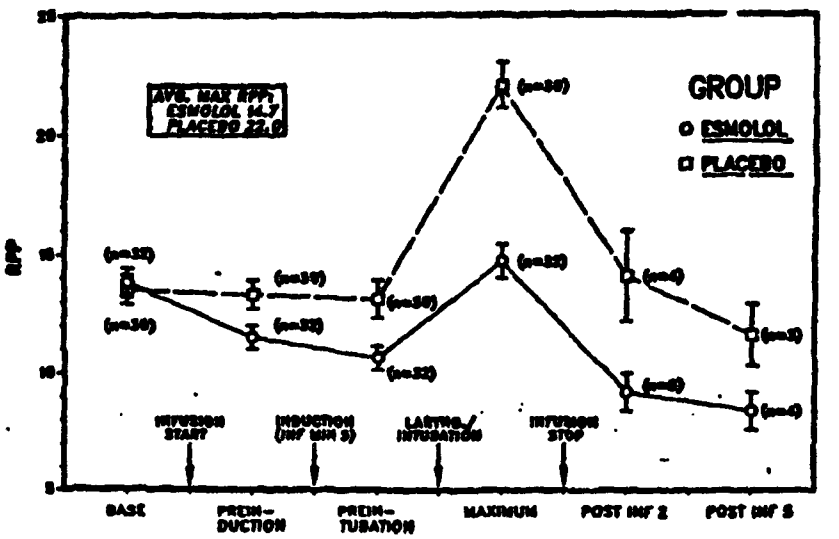
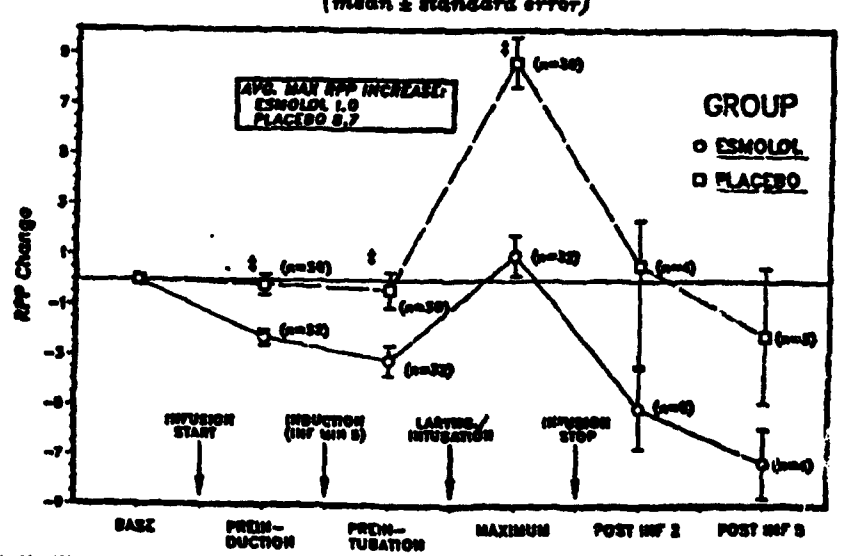


FIGURE 11

Rate–Pressure Product Changes from Baseline
(mean ± standard error)



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

(c) Clinically significant increases in heart rate and systolic blood pressure. (Table 15) According to the sponsor "following endotracheal intubation, a significantly higher percentage of patients demonstrated heart rate greater than or equal to 100 bpm in the placebo group (60%) than in the esmolol treated group (3%, p less than 0.01). In addition, a significantly higher percentage of placebo treated patients (80%) demonstrated a systolic blood pressure greater than or equal to 180 mm Hg when compared to the percentage of esmolol treated patients (56%, p less than 0.01). Finally, a significantly higher percentage of placebo treated patients (97%) demonstrated a RPP greater than 14 bpm . mm Hg X 1000 when compared to the percentage of esmolol treated patients (59%, p less than 0.01).

Table 15

Clinically Significant Heart Rate (bpm), and Systolic Blood Pressure (mm Hg), and Rate-Pressure Product (bpm • mm Hg X 1000)

		HR≥100	SBP≥180	HR≥100 AND SBP≥180	HR≥100 OR SBP≥180	RPP≥12	RPP≥14	N
Center[a]	Group							
1 & 4	Esmolol	0	6	0	6	7	6	9
	Placebo	4	5	3	6	6	6	6
2	Esmolol	1	6	1	6	7	6	9
	Placebo	5	8	4	9	9	9	10
5	Esmolol	0	3	0	3	5	4	9
	Placebo	5	7	5		7	7	7
6	Esmolol	0	3	0	3	7	3	8
	Placebo	4	6	3	7	7	7	7
	Group							
Pooled	Esmolol	1	18	1	18	23	19	32
	Placebo	18	28	15	29	29	29	30
	Comparison[b]	P>E**	P>E**	P>E**	P>E**	N.S.	P>E**	

a No significant differences among the centers were detected (p≥0.05).
b P = Placebo, E = Esmol 300 mcg/kg/min, *p<0.05, ** p<0.01

11) Analysis of Efficacy by Center

Primary efficacy analysis above pooled the data from the treatment centers. Therapeutic response rates were also analyzed among the different study centers (Tables 14 and 22, Figures 12 and 13). For HR, SBP, MAP and RPP, statistical significance was attained in 3 of the 4 centers with respect to comparisons of the maximum changes between the two groups (esmolol significantly blunted the increase in HR, SBP, MAP and RPP). In addition, DBP increases were significantly blunted in centers 5 and 6. Although statistical significance was not reached for any of the variables in center 2, differences approaching significance can be observed in Table 22. Figures 12 and 13 provide center by center illustrations for the primary efficacy variables, HR and SBP.

TABLE 14

Maximum Change from Baseline for "Efficacy Patients"

		HR CHANGE (bpm)		SBP CHANGE (mm Hg)		DBP CHANGE (mm Hg)		MAP CHANGE (mm Hg)		RPP CHANGE		
		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		MEAN ± SEM		N
Center[a]	Group											
1 & 4	Esmolol	8.9	3.7	-8.5	10.1	19.8	5.7	10.7	8.8	0.1	1.1	9
	Placebo	23.2	6.3	39.8	5.9	36.7	4.7	35.8	3.9	6.3	1.8	6
2	Esmolol	18.4	5.8	8.7	14.9	23.1	8.8	16.6	9.2	3.6	2.6	9
	Placebo	27.8	8.2	44.8	11.6	34.8	4.4	38.8	7.0	8.2	2.1	10
5	Esmolol	10.8	3.8	18.8	9.7	31.0	5.1	28.0	6.2	2.8	1.9	8
	Placebo	28.8	6.8	63.8	8.8	47.2	5.1	52.2	5.8	11.2	1.7	7
6	Esmolol	2.7	4.1	-8.5	9.1	14.5	5.2	5.8	6.8	-1.8	1.1	8
	Placebo	15.5	7.3	33.4	13.8	32.8	8.2	22.5	8.8	5.8	2.3	7
	Group											
Pooled	Esmolol	7.8	2.5	1.6	5.8	21.8	3.8	14.8	3.8	1.8	0.8	32
	Placebo	24.2	3.2	45.8	5.8	37.5	2.8	38.2	3.5	5.7	1.8	30
	Comparison[b]	P>E**		P>E**		P>E**		P>E**		P>E**		

a Significant differences among the centers were detected for HR ($p<0.05$).
b P = Placebo, E = Esmolol 300 mcg/kg/min, *$p<0.05$, **$p<0.01$

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Table 22

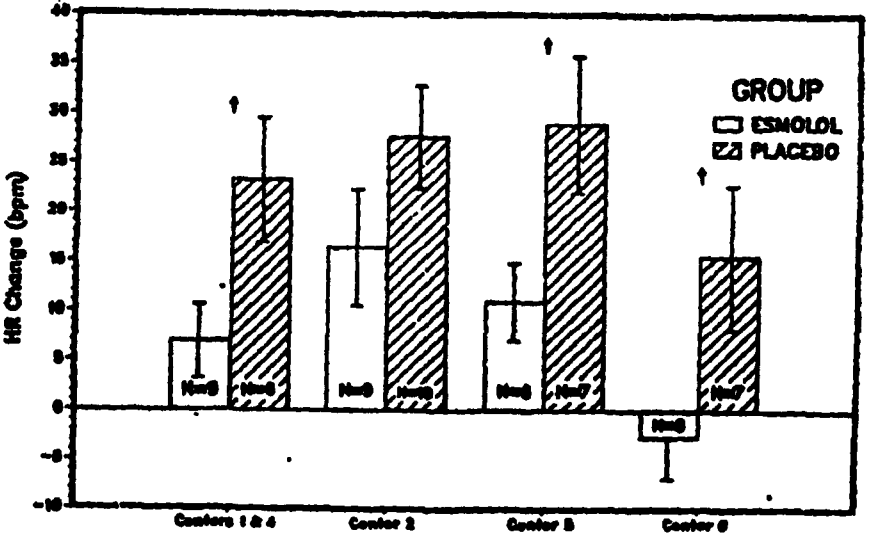
Maximum Change from Baseline for "Efficacy Patients", by Center and Treatment

		HR Change (bpm)	SBP Change (mm Hg)	DBP Change (mm Hg)	MAP Change (mm Hg)	RPP Change	
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	N
Center	Group						
1 & 4	Esmolol	6.9 3.7	-6.5 10.1	10.8 5.7	10.7 6.8	0.1 1.1	9
	Placebo	23.2* 6.3	38.8* 5.9	36.7 4.7	36.8* 3.9	6.3* 1.8	6
2	Esmolol	16.4 6.9	6.7 14.9	23.1 6.8	16.6 9.2	3.8 2.8	9
	Placebo	27.6 5.2	44.5 11.6	34.6 4.4	36.8 7.0	9.2 2.1	10
5	Esmolol	10.9 3.9	16.8 9.7	31.0 5.1	28.0 6.2	7.6 1.3	8
	Placebo	28.9* 6.3	69.6* 8.8	47.2* 5.1	52.2* 5.6	11.2* 1.7	7
6	Esmolol	-2.7 4.1	-8.5 9.1	14.8 5.2	5.8 6.0	-1.6 1.1	8
	Placebo	15.5* 7.3	33.4* 13.9	32.6* 6.2	32.5* 8.6	8.9* 2.3	7

* Indicates significant difference between the esmolol and placebo treatment groups ($p<0.05$).

FIGURE 12

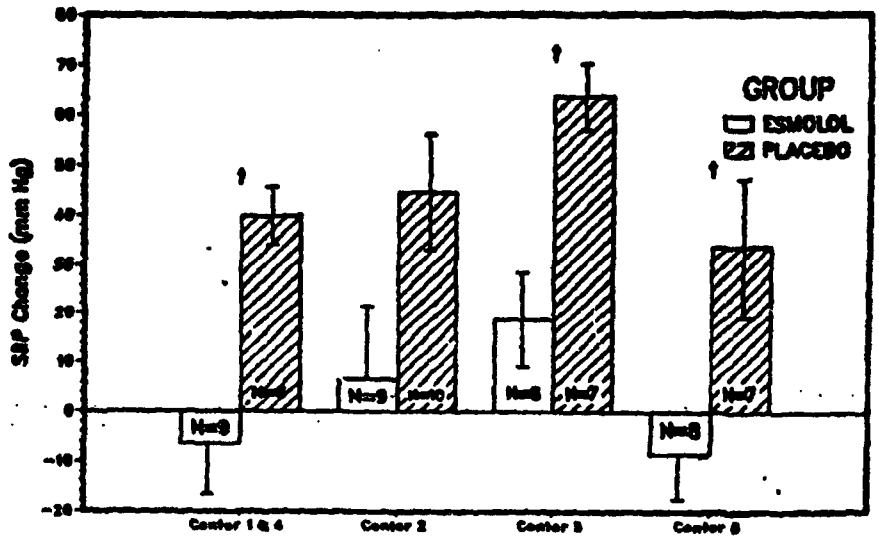
Maximum Heart Rate Changes from Baseline, by Center
(mean ± standard error)



† Significant difference between esmolol and placebo treatment groups ($p<0.05$).

FIGURE 13

Maximum Systolic Blood Pressure Changes from Baseline, by Center
(mean ± standard error)



† Significant difference between esmolol and placebo treatment groups(p<0.05).

III Safety Results

(a) Adverse Effects

According to the sponsor there were no significant differences between treatment groups, between age groups (less than 65 or greater than 65 years) or between sexes with respect to the incidence of adverse effects. Table 32 lists all reported adverse effects arranged by body system and as related to onset time (see Table below). 28 adverse effects were reported during the course of the study for 18 (24%) of the 74 "all patients". Nine patients on esmolol (12%) and 9 patients on placebo (12%) were reported as having adverse effects. The most frequently observed adverse effects related to the cardiovascular system. Eight of the 37 patients treated with esmolol and 8 of the 37 patients treated with placebo were reported to have cardiovascular symptoms. The most frequently reported adverse effect in patients on esmolol was hypotension (in 5 patients). However, 5 patients on placebo also were reported to have hypotension. It is probable that the actual incidence of hypotension was under-reported due to the incomplete data collection (post infusion timepoints 10 and 15 minutes were dropped from analysis and post infusion times 2 and 5 minutes were excluded from analysis). Other adverse effects reported in patients on esmolol were ST-segment depression in one patient (number 229), hypertension in one patient (number 602), junctional rhythm in one patient (number 617) and myocardial ischemia in one patient (number 617).

TABLE 32

ADVERSE EFFECTS BY BODY SYSTEM AS RELATED TO STUDY PERIOD

Patient Number (Group)	Body System	Onset of Symptom		Reference Time		
		Infusion minute	Postinfusion minute	Start Induction min*	Start Intubation min*	Start Isoflurane Inhalation min*
	Cardiovascular					
228(E)	ST-segment depression		10	5.5	7	8
229(E)	ST-segment depression		15	5.5	7	8
502(E)	Hypotension	6.5		5	8	10.5
505(P)	Hypotension		2	5	8.75	9
506(P)	Hypotension		2	5	7.75	8
508(E)	Hypotension		10	5	8.75	9.5
511(E)	Hypotension		2	5	9.25	11
607(P)	Hypotension	9.5		5.5	6.75	7.5
	Hypotension		8.5	5.5	6.75	7.5
608(E)	Hypotension		5	5	6.5	3*
613(E)	Hypotension	8.5		5.5	7.5	7.75
618(P)	Hypotension	11		5	6.75	7.5
620(P)	Hypotension		6	5	7	9
505(P)	Hypertension	8		5	8.75	9
506(P)	Hypertension	8		5	7.75	8
510(P)	Hypertension	8		5	8.25	8.75
513(P)	Hypertension	10		5	9.5	9.75
602(E)	Hypertension	3#		5	10.5	11
620(P)	Hypertension	8.5		5	7	9
617(E)	Myocardial ischemia	7		5	8.25	8.5
505(P)	Tachycardia	8		5	8.75	9
614(P)	Tachycardia	8		5	7.5	7.75
620(P)	Tachycardia	8.5		5	7.5	7.75
620(P)	Bradycardia		6	5	7	9
613(E)	Junctional Rhythm	8.5		5.5	7.5	7.75
	Respiratory					
214(P)	Wheezing		2.25	5	6	6.5
504(E)	Bronchospasm	8		5	7.5	8
	CNS					
602(E)	Agitation	3#		5	10.5	11

(E) Esmolol infusion (P) Placebo infusion
* in relation to start of infusion
+ in relation to stop of infusion
# 500 mcg/kg/min "loading dose"

(b) EKG Results (ST-Segment Changes):

Eleven patients (4 placebo and 7 esmolol treated) exhibited ST-segment changes during the study period. Four esmolol treated patients developed ST-segment depressions-all four consistent with myocardial ischemia (patient 229 required a nitroglycerin infusion and cancellation of surgery; patient 617 developed pseudonormalization of the ST segment but required no treatment; patient 602 developed 2 mm ST segment depression after receiving esmolol 500 mcg/kg/min for 12 minutes instead of 4 minutes; patient 613 developed ST segment depression associated with hypotension and a junctional rhythm. The onset of the ST segment changes for the above patients occurred during the infusion (patients 602, 613, 617) and 10 minutes post infusion (patient 229). (See Appendix 2D for case report summaries) Although 4 patients on placebo developed ST segment changes, these changes were classified as minor and not indicative of myocardial ischemia. Two additional patients had significant ST segment changes during the esmolol infusion but had changes at baseline. However case #619 appeared to develop new ischemic during the study period (ST segment upsloping was noted). Thus the incidence of ischemia may be as high as 5/32.

(c) Patients Terminated Due to Adverse Effects:

Of the 74 patients treated, the sponsor states that only 1 patient (patient 607 in the placebo group) was discontinued due to an adverse effect (severe hypotension requiring CPR). However patient 229 in the esmolol group developed significant ST segment depression and decreased SBP (197-108) during the post infusion. Treatment with Wyamine and a nitroglycerin infusion was required and surgery was cancelled. Other than patient (229) however there is no data regarding the number of patients who had surgery cancelled as a result of adverse effects such as hypotension and/or ST segment changes. Based on the EKG data one can only surmise that a number of additional patients probably had their surgery cancelled. (The sponsor has been asked to furnish this information.) This data is necessary to assess impact on surgical outcome or clinical outcome.

(d) Clinical Safety Variables (SBP, DBP, MAP, RPP):

Unfortunately due to the sponsor's decision to drop analysis at the 10 and 15 minute post infusion periods and to exclude "efficacy data" from "efficacy patients" at the 2 and 5 minute post infusion time points, there is insufficient data available regarding the above parameters to allow for meaningful analysis. However, it is reasonable to infer that the actual incidence of significant changes in these parameters in the esmolol treated group would be considerably higher. The data reported in Table 11 for example tends to support this notion since the SBP in the esmolol treated group is significantly lower from the baseline at post infusion 2 and 5 minutes. Again, the sponsor has been asked to furnish this data.

Addendum to Safety Results/Study 49

In response to our request for information re clinical outcome of patients involved in Study 49 (carotid endarterectomy), the sponsor has submitted a new table "Outcome of All Patients."

OUTCOME OF ALL PATIENTS

POST INFUSION EVENT	Treatment Group: Esmolol # of Patients (Patient No's.)	Placebo # of Patients (Patient No's.)
No problems intraoperative or postoperative	24	22
Intraoperative or postoperative problems		
- Arrhythmias	5 (504, 603, 606, 613, 624)	5 (404, 607, 610, 618, 620)
- Ischemic changes	2* (229, 240)	1 (404)
- Myocardial infarctions	1** (206)	1 (514)
- CVA	2 (218, 236)	1 (513)
- Deaths	0	2 (229, 212)
- Cardiac enzymes elevated	1 (504)	2 (512, 513)
- Right bundle branch block	0	1 (513)
- Respiratory distress and hives	0	1 (510)

* These patients had ischemic changes intraoperative.
** This patient experienced a myocardial infarction intraoperative.

Note: Three patients experienced multiple problems.

Review of this data reveals similar array of ADE in both treatment groups although the incidence of ischemic changes and CVA are higher in the esmolol group. Since the numbers are so small it is not really possible to assess whether there is no difference in the incidence of ADE or clinical sequelae in the two treatment groups. It is probably more accurate to say that the data doesn't allow one to show the true size of the difference if one is truly there. (See biostatistics analysis.)

Overall Results and Conclusions of Brevibloc Efficacy and Safety

Second Indication

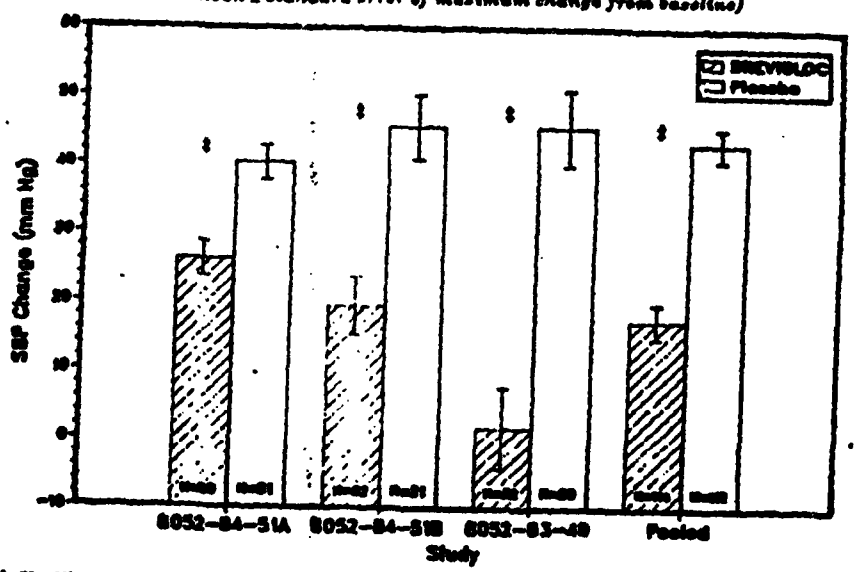
B. Management of Perioperative Tachycardia and Hypertension Induced by Endotracheal Intubation

(1) Efficacy

Although two of the three dose ranging pilot studies of esmolol in the management of tachycardia and hypertension did not show a clear effect or a dosage-response relationship trend (none of the three dose ranging studies showed statistically significant differences in primary efficacy

variables) but did show a good safety profile at all dosages, only a single dosage was employed in the controlled clinical studies. The sponsor decided that individualization of dosage by titration was not feasible in the perioperative setting since the drug was given to blunt the effects of a rapid and significant stimulus induced endogenous catecholamine release. In three well controlled multicenter, randomized, double-blind placebo controlled studies [51A, 51B, 49 (Study 51 was reported as 2 separate studies) esmolol [(500 mcg/kg/min loading dose - 300 mcg/kg/min maintenance dose)] was found to in inhibit the maximum increases in HR, SBP, MAP, and RPP following endotracheal intubation in noncardiac surgery patients (51A and 51B) and patients undergoing carotid artery surgery (49). Esmolol also prevented clinically significant increases in heart rate (greater than or equal to 100 bpm) and systolic blood pressure (greater than 180 mm Hg) when compared to placebo. A summary of these 3 studies and the overall results are provided in the following 3 figures (HR change, SBP change, and RPP change). Since the study design for all three studies were virtually the same, the data from all three studies have been pooled for this overall evaluation.

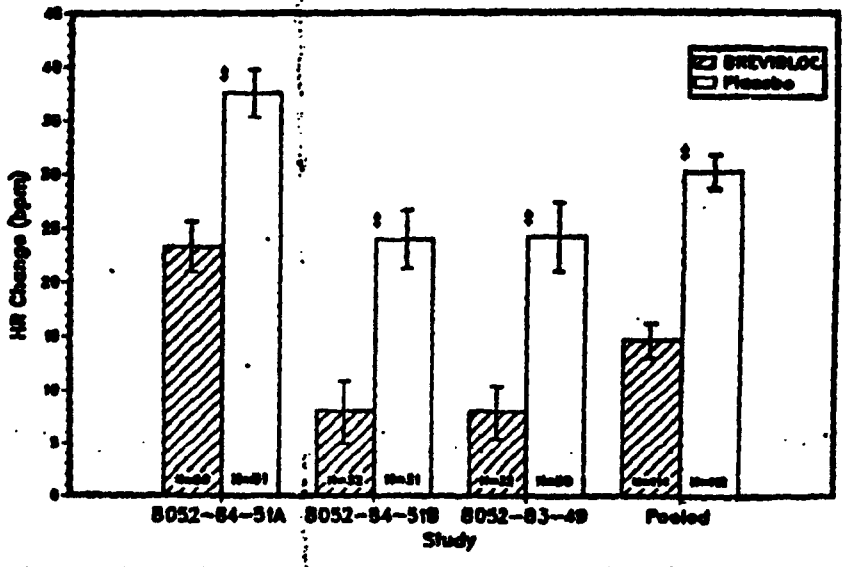
Figure
Attenuation of Intubation-Induced Increases in Systolic Blood Pressure by BREVIBLOC
(Results from three well-controlled multicenter studies:
mean ± standard error of maximum change from baseline)



‡ Significant difference between esmolol and placebo treatment groups ($p<0.01$).

Figure

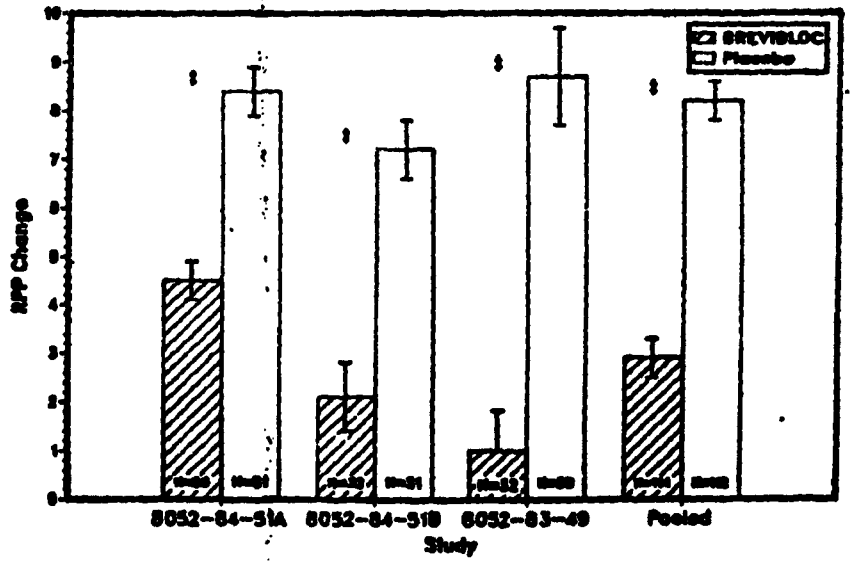
Attenuation of Intubation-Induced Increases in Heart Rate by BREVIBLOC
(Results from three well-controlled multicenter studies: mean ± standard error of maximum change from baseline)



‡ *Significant difference between esmolol and placebo treatment groups($p<0.01$).*

Figure

Attenuation of Intubation-Induced Increases in Rate-Pressure Product by BREVIBLOC
(Results from three well-controlled multicenter studies: mean ± standard error of maximum change from baseline)



‡ *Significant difference between esmolol and placebo treatment groups($p<0.01$).*

Analysis and Comment

1. However, due to the sponsor's arbitrary decision to exclude partial efficacy data from the majority of patients (in all three trials) due to changes in the inspired dose of inhalation anesthetic agent, serious problems arise in terms of assessing the efficacy and safety of esmolol during the entire course of the study. Clearly at the study points analyzed by the sponsor (particularly the maximal change post intubation, the effects of esmolol on HR and SBP are quite clear. However, all study points thereafter including the post infusion study period have been excluded from analysis or analyses have been limited to a very select few patients. Based on the ADE especially observed in study 49 (see safety section) the positive effect on HR and SBP is associated with potential risk and adverse effects which tend to lessen enthusiasm for general application of this intervention without sufficient data regarding clinical safety variables during the entire study period.

2. Another major concern (in all three trials) is the lack of prospective data and/or information regarding clinical (surgical outcome) in the two treatment groups. Thus the sponsor's entire claim for efficacy and safety is based on a truncated analysis of two parameters of beta blockade namely HR and SBP and clinical safety variables (MAP, DBP and RPP). Since there is no data or analysis of clinical outcome derived from the intervention (beta blockade with a short acting beta blocker during endotracheal intubation) the assessment of therapeutic benefit is really based on extrapolating the sponsor's premise to the results obtained in the clinical trials. In essence the sponsor's rationale is predicated on the supposition (inferred from limited clinical and experimental data) that blunting or preventing the adrenergic mediated reflex hypertension and tachycardia elicited by endotracheal intubation (and surgery) will significantly reduce the development of myocardial ischemia and/or infarction in surgical patients especially in those with coronary (carotid) artery disease. Hence the sponsor concludes that the positive effects of esmolol on HR, SBP and RPP means "a significant increase in myocardial work would be minimized or prevented in a situation where such an increase is undesirable." However, even if one accepts the premise that blocking catecholamine mediated hypertension and tachycardia is desirable in certain patient subgroups or in most patients for that matter, there is only partial efficacy data regarding one study time point upon which to assess "efficacy" in an adequate number of patients. On the other hand, if the sponsor's premise is not accepted, then there is no real efficacy data regarding esmolol mediating improvement in surgical or clinical outcome in these patients. In any event, the data presented addresses only the question whether esmolol functions as an active beta blocking agent i.e., increasing the functional AV refractory period and inhibiting the hypertensive effects of catecholamines. Based on the limited data and the analysis presented, esmolol does appear to have a positive effect in attenuating the increase in HR and SBP associated with endotracheal intubation.

Recommendation for Anesthesia Studies

Based on the considerations discussed above and safety issues addressed below, approval for this indication is not recommended. The overall deficiencies and/or problems leading to this decision are summarized as follows:

1. Only one major efficacy/safety timepoint (i.e., maximal change after intubation) was provided for the "efficacy patients." The other time points (i.e., post infusion) were excluded in the majority of patients.

2. It is not known whether this single timepoint is the best or most appropriate way to measure the desired response. It may be better to integrate or average the HR and SBP response over the infusion period ± post infusion period.

3. There is essentially no prospective data re clinical or surgical outcome in all three studies (no hard endpoints).

4. In Study 49 there is evidence of myocardial ischemia in the esmolol treated group (four cases vs none in placebo). Also the outcome of "all patients" in Study 49 suggests there may be worse outcome with esmolol. However, the relatively small patient numbers in the treatment groups doesn't allow one to show the true size of the difference if one is truly there.

5. The sponsor's rationale for using esmolol in this setting has never been confirmed by a prospective randomized clinical trial. Therefore it is not known whether efficacy in this setting can be equated with beta blockade per se.

6. The dose ranging pilot studies and clinical efficacy trials have not established a dose-response relationship with respect to objective response (↓HR and ↓SBP) or ADE (side effects).

7. Overall impression of the results of anesthesia studies (those reported in the NDA and others published in the medical literature) and the perioperative efficacy trials (especially study #49) suggest there may be important differences in the efficacy, safety and predictability of esmolol as a function of the type of anesthetic agent as well as patient population. While the effects of esmolol appear to be safe and predictable when used in combination with IV anesthetics, its effects on clinical safety (hemodynamic) parameters when combined with inhalatorial agents may be marginal and less predictable. Further, questions regarding the use of esmolol perioperatively in patients who are hypertensive, who have impaired ventricular function and patients who are taking chronic beta and calcium channel blocking agents need to be answered.

8. The benefits do not clearly outweight the risks since (a) the sponsor hasn't established a dose-response relationship to ADE (and there are side effects) and (b) the sponsor hasn't clearly established an appropriate effective dose (it isn't known that a lower dose would work).

(11) Safety

The overall incidence of ADE reported by the sponsor in the 3 clinical trials was quite low. However, there are several safety issues raised by these studies. First, the actual incidence of cardiovascular ADE particularly hypotension is probably significantly understated in these trials. As previously alluded to, the sponsor has arbitrarily excluded an analysis of partial efficacy data in clinical safety variables in these studies. Moreover the trends in SBP and HR for the few patients reported by the sponsor especially at 2 and 5 minutes post infusion suggest that the incidence of hypotension might be considerably higher if "all patients" and all data points were included in the analysis. The sponsor has been asked to furnish the excluded data. Second, the ADE reported in study 49 are very provocative. While there were no apparent quanitative differences between the treatment groups, there were real qualitative differences in ADE reported. Of particular interest was the association of significant ST segment depression (indicative of ischemia) in the esmolol treated group (7 patients). Four of these 7 patients had changes consistent with myocardial ischemia and had onset either during the infusion or 10 minutes post infusion. Development of myocardial ischemia is a particular concern in these patients since if the sponsor's rationale is correct, esmolol should if anything reduce or prevent ischemia. It would also be of considerable interest to know the clinical or surgical outcome of the esmolol treated patients compared to the placebo group. In summary, several safety related issues have arisen during the perioperative clinical trials which are of concern. It would be desirable to have access to the excluded efficacy data and clinical safety variables so that the actual incidence of ADE, especially hypotension, bradycardia and abnormal EKG changes can be ascertained. In addition, it is important to quanitate the number of patients who were prematurely terminated from the trial or from subsequent surgery as a result of ADE. Review and analysis of this data would be essential if we are to adequately assess the safety i.e., benefit to risk ratio for esmolol particularly in the patients with CAD and carotid artery disease who are prime targeted populations for esmolol.

Addendum to Safety (Studies 51A, 51B, 49)

In response to our request for data that was excluded from the efficacy analysis in the anesthesia studies, the sponsor has submitted amended and new tables. (See Appendix 2E.) However, many of the same problems identified in the NDA are again noted in the "new tables." For example, the sponsor has again excluded data re efficacy and safety variables in the majority of patients classified as "efficacy patients." Thus the data at the following timepoints are incomplete and unevaluable: post infusion 2, 5, 10 and 15 minutes. In general, the sponsor has included data from more patients at these timepoints in the tables for "all patients" (except for the 15 minute point in Studies 51A and 51B in which 25 to 40% of "all patients" have still been excluded.

In studies 51A and 51B HR but not SBP is significantly different in the two treatment groups through the 10 minute post infusion point. In contrast, in study 49 both HR and SBP are significantly different up to and including 10 minute post infusion. The nadir of the SBP is approximately 100 mm Hg for both treatment groups in studies 51A and 51B (versus baseline values of 130-140). The nadir of the SBP is 122 (versus baseline 182) in study 49 for the esmolol group. Thus in study 49 the relative decrease in SBP is greater in the esmolol group although the absolute level does not reach criteria hypotension.

While the data reported in these tables support the view that esmolol does not induce clinical hypotension in the majority of patients enrolled in these studies, the exclusion of between 25 to 40% of "all patients" in studies 51A and 51B give cause for concern. Since this data has not been included, we just don't know what happened to these patients in terms of clinical safety variables (SBP, DBP, MAP, RPP etc). Moreover, the rate and relative extent of change in SBP or RPP may be as meaningful as absolute levels especially in patients with CAD. Furthermore, the sponsor has really provided only one data point (maximal change) during the study period. However, the major determinant of response or benefit may be better estimated by measuring the average SBP or HR integrated over the entire study period rather than just relying on one data point to assess response. Unfortunately, there is no information or data which addresses this point.

Ronald Lieberman

Ronald Lieberman, M.D.

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SECTION .I - AMENDMENT TO NDA 19-386, BR. IBLOC

This amendment concerns the final reports of two additional clinical studies which were in progress at the time of initial submission of NDA 19-386 on January 7, 1985. These studies are as follows:

Study 8052-83-27 "Effect of esmolol vs placebo on heart rate and blood pressure during specified surgical stimuli in anesthetized coronary revascularzation patients: a multicenter trial"

Number of Patients Entered: 43 esmolol; 41 placebo; 18 standard therapy

Study 8052-84-56 "Effect of esmolol vs placebo on hemodynamics and myocardial ischemia during specified surgical stimuli in anesthetized coronary revascularzation patients - J. Erol Wynands, M.D.

Number of Patients Entered: 15 esmolol, 15 placebo

As a result of discussions with Dr. Lipicky on January 9, 1986, the sponsor has agreed to submit these reports and to incorporate them into the draft summary basis of approval (SBA). These reports are being submitted to the FDA to be reviewed by the division (See Medical Review NDA 19-386).

A. OVERVIEW AND SUMMARY OF TWO ADDITIONAL CABG STUDIES

These two additional studies 8052-83-27 (multicenter trial) and 8052-84-56 (single institutional trial) involving perioperative use of esmolol in patients undergoing CABG surgery have been submitted by the sponsor in support of NDA 19-386. The studies are being submitted with a view toward addressing concerns regarding the efficacy and safety of esmolol (i.e., un-anticipated incidence of myocardial ischemia (5 of 32 patients) noted in study 49 involving carotid artery surgery).

1. Efficacy: These two studies are very similar in terms of objectives, design, treatment schedule and dose, patient selection and response criteria. Both were prospective, randomized, double-blind, placebo controlled, parallel clinical trials aimed at demonstrating that esmolol safely and effectively controls the catecholamine mediated hypertension and tachycardia that occurs during specific surgical stimuli (intubation, skin incision, sternotomy and aortic dissection). Study 56 also hoped to quanitate the relative incidence of myocardial ischemia in the two treatment groups. In addition, the use of supplemental anesthesia and other medical interventions was also assessed. In spite of the basic similarities in these studies, the efficacy results are somewhat different. In study 27 the major finding was that esmolol attenuated the heart rate response at intubation and aortic dissection. In addition, patients on esmolol required less supplemental anesthesia. In contrast, the major result in study 56 was that esmolol altered the SBP response at sternotomy and that there was no significant difference in myocardial ischemia

in the two treatment groups. Moreoever, in study 56 there is neither a difference nor a positive trend in favor of the esmolol group at intubation with respect to HR response. Although statistically significant, there is question as to the clinical importance of the small absolute changes observed in the heart rate response at aortic dissection (study 27) and systolic blood pressure (SBP) response at sternotomy (study 56). In fact, these changes are probably of no clinical significance (see discussions below). It is important to note that results of the "all patients" analysis in Study 27 provides much more favorable profile of esmolol efficacy compared to the "efficacy patients" analysis. In essence, the esmolol treated patients had more favorable outcomes in terms of control of tachycardia (HR) and hypertension (SBP) during the specified surgical stimuli than did the placebo treated group. However, since most of the increase in HR response occurred at preintubation (prior to intubation) (Table 36) the efficacy of esmolol in blunting the adrenergic stress at intubation per se is not as impressive as it appears. The results at intubation are further complicated by the fact that SBP went in the opposite direction at preintubation (SBP actually decreased in both groups whereas HR increased). One explanation for this pattern of response is that patients are undergoing significant vasodilation and the tachycardia is a compensatory response to the hypotension. Although the reason(s) for the differences in efficacy results between the two studies is not entirely clear, examination of the two studies does indicate several points of difference which are outined in Table 1 below.

TABLE 1
[COMPARISON OF TWO CABG STUDIES (27 vs 56)]

	Study Parameters	Study 27 (Multicenter)	Study 56 (Single Center)
1.	# Patients Randomized (Esmolol vs Placebo)	43 vs 41 18 Std Rx Group (Nonrandomized)	15 vs 15
2.	Loading/Maintenance Doses of Esmolol	E500X2'; 200-CPB	E500X4', 300-CPB
3.	Time of Induction After Start of Esmolol	5'	10'
4.	Loading/Maintenance Doses of Inducing Agent	Fentanyl 50 mcg/kg-PRN or Valium 0.5 mg/kg	Fentanyl 40 mcg/kg- .4 mcg/kg/min
5.	Supplemental Inhalational Anesthetic	Halothane or Enflurane PRN	Isoflurane PRN
6.	Concurrent Ca^{++}/ Beta Blockers	No (Yes Std Rx Group)	YES
7.	Definition of Ischemia	1 mm ST segment ↓ or ↑ greater than 1 min	1 mm ST segment ↓ or ↑ greater than 10 seconds
8.	Onset of Ischemia	Various times during study (intubation, aortic dissection)	Only at aortic dissection
9.	Efficacy Result (1° Endpoint)	↓ HR at intubation, aortic dissection	↓ SBP at sternotomy
10.	CVADE: Ischemic	E 2/43 PBO 4/41 STDRx 4/18	E 1/15 PBO 3/15
	Hypotension	E 2/43 PBO 0/41	E 4/15 PBO 3/15

2. Safety (ADE): In both studies the major ADE appeared similar. Cardiovascular ADE predominated in both with hypotension and ischemia as the major side effects. In both CABG studies the incidence of myocardial ischemia appeared low and there was no statistically significant difference in the overall rate of ischemia between esmolol and placebo groups. Curiously in study 56, all cases of ischemia occurred at aortic dissection whereas in study 27 ischemia occurred at various times throughout the study period. The relative incidence of myocardial ischemia in study 27 as defined by EKG criteria appears to be similar in the two study groups: 4 out of 41 (placebo) vs 2 out of 43 (esmolol) (three of the four placebo patients (104, 511, 119) exhibiting ischemia during the study period also had ischemic changes during the baseline period prior to the start of the study see appendix 11). In essence, the use of esmolol in these two CABG studies does not appear to be associated with either an increased benefit or an increased risk regarding the occurrence of new myocardial ischemia/injury events. In addition, since the incidence of myocardial ischemia was four out of 18 (greater than 20%) in the nonrandomized standard therapy group even though those patients were maintained on their calcium channel blockers and beta blockers, there is a suggestion that IV fentanyl anesthesia per se may be contributing to the safety (low incidence of ischemia) in the randomized patients (study 27). This latter point is further supported by the fact that the expected incidence of perioperative myocardial ischemia in CABG patients is much higher (Slogoff and Keats reported an incidence of 37% in 1023 patients undergoing elective CABG operations) [see reference #19 page 100 NDA].

B. Study 8052-83-27

I Description of Study

1. Study Objective: The principal objective of the study was to evaluate the effect of esmolol (200 mcg/kg/min) vs placebo on increases on heart rate and blood pressure during specific surgical stimuli in anthestized patients undergoing CABG surgery. Also to assess the need for supplemental anesthesia and additional therapeutic agents to control the heart rate and blood pressure between the treatment groups.

2. Investigators and Institutions: This was a multicenter study with five investigators finally participating in the study, (although six centers were originally selected to participate in the study center #4 the University of Iowa withdrew). For a complete listing of investigators, institutions and the number of patients enrolled in each center, see Table 1.

3. Study Design: The design of this study was double-blind, randomized, parallel, placebo controlled, prospective, multicenter clinical trial. All randomized patients received an intravenous infusion of either esmolol or placebo which started five minutes prior to induction of anesthesia and in patients whose hemodynamics were well maintained was continued throughout intubation, skin incision, sternotomy and aortic dissection up until five minutes after the start of aortic dissection or until the start of cardiopulmonary by-pass (CPB). A third group of patients receiving standard therapy also was included. This group consisted of those patients who were taking beta blocking agents, calcium channel blocking agents or both, and received a dose of that beta blocker or calcium channel blocker the morning of surgery. These patients received the institution's standard therapy in place of the study drug infusion and were not randomly selected. In contrast, the randomized patients did not receive their morning dose of either calcium channel blocking agent or beta blocking agents.

4. Treatment Plan and Response Criteria: Patients were premedicated approximately 90 minutes prior to the induction of anesthesia. Infusion of the study drug consisted of 500 mcg/kg/min loading dose for two minutes followed by maintenance infusion of 200 mcg/kg/min. Anesthesia was induced with fentanyl or diazepam (each center was allowed to administer its standard anesthetic regimen. Supplementation of anesthesia consisted of primarily halothane or enflurane. Heart rate and blood pressure were recorded during the study (see Appendix I for the anesthetic techniques used at each center). See Table 2 for the schedule of observations and the overall protocol schema.

5. The study consisted of the following periods (see Table 2).

   a. Prestudy evaluation period

   b. Preinfusion baseline period

   c. Esmolol/placebo infusion period

   d. Post infusion follow up period

6. Patient Selection: Patients considered for entry into the study were drawn from a population scheduled to undergo general anesthesia for elective CABG surgery.

7. Number of Patients/"All", "Efficacy", "Dropouts" and "Exclusions": 102 patients (43 esmolol, 41 placebo, 18 standard therapy patients) were entered into this multicenter study. Of these 102 "all" patients, 96 were classified "efficacy" patients, 43 esmolol-treated, 38 placebo-treated and 15 standard therapy. Analysis of the effect of esmolol and placebo on heart rate and blood pressure and other efficacy variables were performed on 96 "efficacy" patients. Safety was based on the data from all 102 patients. See Table 5 for derivation of "all" patients, "efficacy" patients and randomized "efficacy" patients in the study. See Table 6 for a summary of "all" patients at each phase of the study. See Table 7 for a list of patients excluded from the efficacy analysis. As can be seen from Table 7 data from six patients (201, 509, 511, 503c and 505c, 506c were excluded from efficacy analysis. Exclusion of these six patients left 96 patients whose data were subjected to either partial or complete efficacy analysis.

Partial Exclusion of Efficacy Data: Although medical intervention for patient care was not a protocol deviation, a number of "efficacy" patients had part of their data excluded from efficacy analysis because of medical interventions for example nitroglycerin, nitroprusside or propranolol, etc. that according to the sponsor confounded the interpretation of the hemodynamic data collected subsequent to the intervention. Data were excluded from efficacy analysis for the following time periods (see Fig. 1).

Reviewer's Note: Six other patients were not included in portions of the efficacy analysis because of failure to complete the entire study. Three patients (614 and 616 placebo treated; and 620 esmolol treated) were withdrawn from the study because of an adverse reaction. A seventh patient (117 placebo treated) was withdrawn from the study at the investigator's discretion because administration of enflurane during induction, however, the PCC allowed inclusion of efficacy data in this case. Three patients (206 and 612, esmolol treated; 513, placebo treated) failed to complete the study because of the study drug infusion was exhausted prior to the patient's completion. A schematic display of the data included for efficacy analysis is shown in Figure 1. In all 44 of the 96 "efficacy" patients had partial heart rate and blood pressure data excluded subsequent to medical intervention. Medical intervention was not a protocol violation and many of the same agents were classified as therapeutic medical interventions to control heart rate and blood pressure anyway. Since this data has been included in a "all" patient efficacy analysis, it will be important to compare these two data sets.

8. Efficacy Assessment: Efficacy in the study was defined as the attenuation of increases in heart rate, blood pressure and rate pressure product by esmolol in comparison to placebo during specified surgical stimuli. In addition the frequency and amount of supplemental anesthesia in addition to therapeutic agents required to control heart rate and blood pressure in the esmolol and placebo treated groups were compared. Thus primary efficacy variables were (a) maximum changes in heart rate, systolic blood pressure and rate pressure product vs surgical stimuli; (b) frequency and amount of supplemental anesthesia in addition to therapeutic interventions. Secondary efficacy variables were (a) maximal changes in diastolic blood pressure and mean arterial pressure; (b) clinically significant increases in heart rate and blood pressure; (c) exceeding ischemic thresholds and (d) comparison of the standard group to the randomized group.

II Study Results

A. Baseline Demographics and Comparability of Treatment Groups: As documented in Tables 9, 10 and 13 there were no significant differences for age, height, weight, heart rate, systolic blood pressure and diastolic blood pressure as a function for treatment group.

8. Efficacy Results: These results are tabulated in Tables 11, 14, 15, 16, 17, 18, 20 for the primary efficacy variables and Tables 21, 22, 23, 24 (supplemental anesthesia), 27, 28 (medical interventions) and 29 (randomized vs standard group therapy). Efficacy results are also found in Figures 2-11 and 12, 13, 14 (standard treatment).

(i) "Efficacy Patients"

Primary efficacy variables as a function of treatment group and specified surgical events. According to the sponsor, esmolol significantly (p less than 0.05) blunted the increases in heart rate when compared to placebo during the stimuli of endotracheal intubation and aortic dissection: the average maximum heart rate increase in placebo patients was 19 bpm as opposed to an average increase of 7 bpm in the esmolol group during intubation; during aortic dissection the maximum heart rate increase was 8 bpm in placebo patients compared to an average decrease of -1 bpm in the esmolol group. It is important to note that statistically significant changes in HR were already apparent at preintubation prior to the time of maximal adrenergic stress (intubation). Since the bulk of the increase in HR occurred prior to intubation, the contribution of esmolol to the overall effect at intubation must be cautiously interpreted (Table 11, Figure 2). This is even more complex since SBP is actually lower in both groups at preintubation compared to baseline. Analysis of rate pressure product revealed findings similar to that of heart rate during endotracheal intubation and aortic dissection. However, there was no significant difference between the esmolol and placebo treated groups with respect to differences in systolic blood pressure although the overall trend was in the right direction (esmolol group lower than placebo group). In addition, the sponsor reports that there were significant differences in the requirements for the amount of supplemental anesthesia and other medical intervention with respect to the two treatment groups. Accordingly the placebo group showed an average of 32.0 Mac units which was significantly greater than the average of 17.7 Mac units for the esmolol group. The esmolol treated group demonstrated a significantly lower proportion of patients requiring therapeutic interventions with nitroprusside and propranolol to control heart rate and blood pressure than did the placebo group. See Tables 21, 22, 23, 24, 27 and 28.

Skin Incisions and Sternotomy: Because of significant center by treatment interactions, changes in heart rate, systolic blood pressure and rate pressure product could not be statistically tested between treatment groups for skin incision and sternotomy (Tables 15 and 16). There was no significant difference between the two treatment groups with respect to changes in systolic blood pressure or rate pressure product during and following aortic dissection.

Diastolic and Mean Arterial Pressure: No significant differences were found between the two treatment groups with respect to maximum changes and diastolic pressure and mean arterial pressure from baseline and intubation and aortic dissection. Due to significant center by treatment interactions, changes in diastolic and mean arterial pressures cannot be statistically tested at skin incision and sternotomy (Tables 11 and 12).

(ii) "All Patients" - Analysis of Maximum Changes in Primary Variables (HR, SBP and RPP) from Baseline

The results of the "all patients" analysis for primary variables are found in Tables 36-42 and Figures 18-23. It is important to note that the results of the "all patients" analysis provides more impressive evidence of esmolol efficacy compared to the "efficacy patients" analysis. (The reason(s) for this difference are not entirely clear).

Summary of Efficacy Results

1) For all events, the esmolol-treated group showed either significantly smaller increases (intubation, sternotomy, aortic dissection) or actual decreases in HR(correct trend though not statistically significant) when comapred to the placebo and standard therapy group (see Table 36).

2) Esmolol significantly blunted the increases in SBP observed during Intubation and sternotomy compared to placebo and standard therapy.

3) Similar results to 1 and 2 were also obtained for RPP.

4) However, similar to what was observed for "efficacy patients," statistically significant changes in HR were evident at preintubation. Since most of the increase in HR occurred prior to intubation, the contribution of esmolol to the net effect at endotracheal intubation must be cautiously ~~by~~ interpreted (Table 36).

5) The interpretation of the results is further complicated by the fact that SBP is not parallel with HR (whereas HR increases at preintubation SBP decreases in both esmolol and placebo groups during preintubation). The reason(s) these two key variables do not change in parallel during the preintubation phrase is vasodilation (induced by fentanyl) (Table 36).

6) The above results suggest that another endpoint (retrospectively) could be the preintubation period. Esmolol appears to significantly blunt the HR response compared to placebo. Since other studies (Slogoff & Keats) have shown that almost half of perioperative ischemia occurs prior to induction of anesthesia, there may be a catechol surge prior to induction of anesthesia which should be controlled. Future studies should consider even earlier intervention with esmolol (perhaps during the baseline period). The weak point in the analysis however is that there are no real hard endpoints to correlate the pharmacological effects of esmolol with clinical (surgical) benefit.

iii) Analysis of Maximum Changes and Hemodynamic Variables from Baseline for Individual Centers: Tables 14-17 provide the data from maximum changes for baseline at each surgical event for the 81 randomized efficacy patients by center. Because of significant center by treatment interactions the data for these hemodynamic variables cannot be compared and show unexpected and paradoxical changes. For example, the heart rate response at intubation orders in a logical manner except for center 5 in which the placebo group showed a lower maximal response than the esmolol group. In addition, the SBP response at intubation in center 5 also shows a reversal (lack of ordering) between the placebo group and esmolol groups. Furthermore, although center 1 did show an appropriate ordering of response for heart rate at intubation, it did not show an appropriate ordering of response for heart rate at skin incision or sternotomy. In addition, it did not show an appropriate ordering of the response for systolic blood pressure at sternotomy. Thus centers 1 and 5 did not show an appropriate ordering of response with respect to heart rate at either intubation, skin incision, sternotomy and aortic dissection. Thus although heart rate and intubation orders in all the centers except for center five, heart rate does not order in centers one and five at other times, such as at skin incision and sternotomy. In addition, although heart rate and aortic dissection does order in these centers, four of the five centers did not show a statistically significant change, although the entire group pooled did show a statistically significant difference. (See the section on analysis and comment for further information regarding the interpretation of the efficacy results.) In addition the sponsor has provided a description and analysis of the changes in the hemodynamic variables for the individual centers which is provided in the appendix.

C. Safety Results - ADE: According to the sponsor, eight (8%) of the 102 "all" patients exhibited adverse effects during the course of the study. Three patients received esmolol (3/43, 7%) and three patients received placebo (3/41, 7%) and the remaining two patients received standard therapy (2/18, 11%). A summary of all adverse effects is provided in Table 50. Details of the adverse effects by body system in each treatment group are given below:

Cardiovascular: Two of the 43 patients treated with esmolol (603 and 620) and three of the 41 patients treated with placebo (316, 614 and 616) had cardiovascular symptoms. In addition, patient 301C in the standard group was reported to have an adverse effect of the cardiovascular origin. Both of the esmolol treated patients 603 and 620 exhibited moderate hypotension. Both of these patients required treated with vasopressors and in addition esmolol was discontinued in the case of patient 620. The cardiovascular adverse effects exhibited by the placebo patients consisted of the following: cardiac arrest (316); ST segment depression (614) and pulmonary hypertension (616). The standard therapy patient with a cardiovascular adverse effect (303C) had ischemic EKG changes.

Respiratory System: One of the standard therapy patients was reported to have sufferred bronchospasm (305C).

Skin: One patient in the esmolol group was reported to have urticaria (118) which appeared to be an allergic reaction to albumin.

The study drug infusion was discontinued prematurely in three patients (614 and 616, both placebo and 620, esmolol) due to adverse effects.

Electrocardiographic Abnormalities: During the study the investigator monitored each patients EKG for abnormalities including ST segment changes and arrhythmias. Forty-six patients (19 esmolol; 20 placebo; 7 control) exhibited EKG abnormalities during the study. Thirty-seven of these patients had EKG abnormalities noted on their prestudy 12 EKGs. Thirty-nine patients who had abnormalities on their prestudy EKGs exhibited no changes during the study. See Table 51 for a combined prestudy baseline and during study findings.

Analysis of ST Segment Changes: Four patients (104, 119, 511 and 614) treated with placebo, four patients (301C, 308C, 309C, 503C) in the standard treatment group and two esmolol treated patients (504 and 514) were noted to have changes in the ST segment during the study under EKG. Patient 504 developed ST segment depression (5 mm) several minutes after aortic cannulation. Heart rate was noted to be 67 bpm and blood pressure was 96/60 mmHg. Patient 514 was noted to have ST-segment depression (2 mm) shortly after induction which occurred again during mammary artery dissection. Heart rate was 63 bpm and blood pressure was 99/46. Therefore, these two cases of ischemia do not appear to be related to a hyperdynamic state such as increased SBP, heart rate or RPP. Reviewer's Note: Somewhere in the material submitted I was able to find that the definition of ischemia in the study was a 1 mm ST segment increase or decrease which lasted greater than one minute. This definition differs from the one used in study 56 the other CABG study. In addition this definition is different from the one used in study 49 and is different from the criteria that the FDA used in its analysis of the ischemic changes in study 49. In that case, ischemia was judged to be present if the ST segment had at least a 2 mm depression or elevation. It would appear from the data presented above that four patients in the placebo group had ST segment changes consistent with ischemia and that at least two patients in the esmolol group had ST segment changes consistent with ischemia. Thus there appears to be no gross difference in the incidence of ischemia in these two groups.

III Analysis and Comment of the Efficacy Results

There are a number of factors which need to be considered in assessing the efficacy results which the sponsor has reported to show statistically significant changes observed in the heart rate response at intubation and aortic dissection. These include the following:

1. The partial exclusion of efficacy data (heart rate and systolic blood pressure) from 44/96 efficacy patients subsequent to medical interventions (although these interventions were not protocol violations). For example, in the esmolol group, the number of efficacy patients progressively diminishes during the course of the study (Table 11). Baseline=43; Intubation=38; Aortic Dissection=33

Ironically, the "efficacy patients" analysis is much less favorable to esmolol than an "all patients" analysis of the data. Therefore, in the section which follows, these differences in the two "data sets" need to be addressed.

In items 2-6, the initial analysis (a) pertains to "efficacy patients" whereas the latter analysis (b) pertains to "all patients."

2. a) "Efficacy Patients" - There is a lack of correlation between the two major efficacy variables (HR and SBP) as only heart rate showed statistically significant changes at intubation and aortic dissection (Table 11). However, the SBP response at intubation is in the right direction (positive trend in esmolol group). This is not true for SBP response at aortic dissection (no difference between the treatment groups). Hence, it is clear that the two primary endpoints (HR and SBP) do not correlate at each of the timepoints defined as surgical stimuli (intubation, aortic dissection).

   b) "All Patients" - In general, the HR and SBP responses show a more favorable trend at intubation and aortic dissection. At intubation, both HR and SBP showed statistically significant changes in the esmolol treated group. However, there is again a lack of correlation at aortic dissection (HR in the esmolol group is positive while SBP shows no real difference).

   Thus if only the results at intubation are assessed, then the results in study 27 compare favorably with the expected results (observed in studies 51A, 51B and 49) in which both SBP and HR were appropriately effected by esmolol and correlated.

3. a) "Efficacy Patients" - There is a lack of parallel changes in HR response with other surgical stimuli such as sternotomy and skin incision (Table 11). One would assume that if esmolol is producing a consistent and significant effect on heart rate then similar changes in HR would be observed with other surgical stimuli. For reasons already discussed under the efficacy results, the sponsor noted profound treatment by center interactions which made this anlaysis untestable.

   b) "All Patients" - In general HR responses at the various surgical stimuli including skin incision and sternotomy show either statistical significance in the esmolol group (sternotomy) or appropriate positive trend (skin incision). It appears from the data that esmolol attenuates the HR response across the spectrum of surgical stimuli.

4. a) "Efficacy Patients" - There is variability of primary efficacy variables in terms of expected ordering of response in a given center. For example, center 5 does not order with respect to HR and SBP at intubation (contrary to the other four centers, the placebo group is lower than esmolol group). See Table 14.

b) "All Patients" - In contrast to the above paradoxical ordering of response at intubation in center 5, the data now shows the expected ordering for these two variables. However, there is still something different about center 5 since it is the only center in which the difference in HR between the two treatment groups is almost neglibible. Yet the anesthetic regimen is almost identical to the majority of the other centers.

5. a) "Efficacy Patients" - The HR change at aortic dissection showed a statistically significant difference in the pooled data. However, only one of the five centers actually showed a statistically significant difference (centers 2 and 3) (Table 17). While statistically significant, the magnitude of the change in HR is so small (a change of 8 bpm from baseline) it is doubtful that this change would be significant clinically.

b) "All Patients" - Although the pooled data showed a statistically significant change in SBP in the esmolol group at intubation (Table 36) analysis by individual centers provides a different picture. Four of the five centers show practically no difference in SBP between the treatment groups (Table 39). In fact only one center (center 1) shows a statistically significant differences. In fact it appears that this center is so different that it probably skews the pooled data (Table 39). It is interesting to note that this was the only center employing IV valium for induction of anesthesia. If center 1 data is excluded, the changes in SBP at intubation would no longer be statistically significant (Table 39).

6 a) "Efficacy Patients" - Significant center by treatment interactions for the primary efficacy variables were deduced by the sponsor at skin incision and sternotomy (Tables 15 and 16).

b) "All Patients" - In the view of the medical reviewer, there appears to be a case for significant center by treatment interactions for the primary variables in center 1 primarily due to the different anesthetic regimen. In addition, the data in center 5 is clearly different from the other centers in terms of HR response at intubation. Whether this data should be omitted from the pooled data is not clear?

7) Analysis of the second part of the primary efficacy criteria (comparison of the use of supplemental anesthesia and other medical interventions to control HR and SBP) shows a consistent trend in favor of the esmolol treatment group. This includes (1) MAC units by center, (statistically significant difference) (Table 21); (2) MAC units by event (Table 22) (significant difference between treatment groups at intubation and aortic dissection); (3) number of patients requiring supplemental anesthesia (no significant differences re enflurance and halothane usage) see Table 23; (4) number of patients requiring therapeutic interventions to control heart rate and blood pressure: placebo 24/41 (58%) vs esmolol 14/43 (33%) (Table 27).

8) Analysis of Outcome Correlates

Analyses were performed on several variables which can be considered "correlates of outcome." Comparisons between treatment groups included (a) length of time on cardiopulmonary bypass, (b) duration the patient required assisted ventilation and (c) the duration the patient was intubated. No treatment differences were observed for any of these variables (Table 43).

9) Comparison with Nonrandomized Standard Therapy

Although the esmolol treated group in general tended to have a lower heart rate than the standard treatment group, (nonrandomized) there was no significant difference in heart rate at intubation between these two groups. Moreover, since there were no significant differences with respect to systolic blood pressure (in fact systolic blood pressure is lower in the standard treatment group at intubation) no clear cut effect of esmolol either beneficial or detrimental can be concluded regarding the comparison of esmolol vs the standard treatment therapy.

C. Study 8052-84-56

I Description of Study

Objective: The objectives of the study were to compare the effects of esmolol 300 mcg/kg/min and placebo on myocardial ischemia and systemic hemodynamics during specific surgical stimuli in patients undergoing CABG surgery who were anesthetized with fentanyl.

Institution and Investigator: The principal investigator for this study was J. Erol Wynands at the Royal Victoria Hospital, Montreal, Canada.

Study Design: Double-blind, randomized, placebo controlled, and parallel.

Treatment Plan and Response Criteria: All patients received intravenous infusion of either esmolol 300 mcg/kg/min or placebo which was started 10 minutes prior to induction of anesthesia and continued until the start cardiopulmonary by-pass. The study drug was administered according to the following schedule: 500 mcg/kg/min for 4 minutes, followed by 300 mcg/kg/min which was continued until the start of cardiopulmonary by-pass. Anesthesia was induced at minute 10 of the infusion with fentanyl 40 mcg/kg i.v. followed by a continuous infusion of 0.4 mcg/kg/min. Isofluorane was administered when supplemental anesthesia was needed. The basic study design and schema was very similar to study 8052-83-27.

Patient Selection: The entry criteria were very similar in terms of the inclusion and exclusion criteria as previously described in study 8052-83-27. However there was one notable exception. Orally or intravenous cardiovascular medications (for example, beta blockers other than nadolol, digoxin, quinidine, procainamide) could be continued provided the doses of such concurrent medications remained fixed throughout the study period. For example, patients could receive their usual dose of chronic oral beta blocker except nadolol up to the morning of the study. Patients receiving calcium channel blockers were originally permitted to the study but a protocol amendment excluded all calcium channel blockers except nifedipine. Nadalol was excluded because of its exceptionally long half life. Nifedipine was permitted because it has only side effects on heart rate, relative to other calcium channel blockers.

Efficacy Assessment: The primary efficacy variables were heart rate, systolic blood pressure and the number of ischemic episodes. Secondary variables were diastolic blood pressure, mean arterial pressure, rate pressure product, the number of arrhythmias and the need for supplemental anesthesia.

Number of Patients - "All", "Efficacy", "Exclusions": Thirty patients were entered into the study and were randomized to either esmolol or placebo. One of these 30 "all" patients was completely excluded from the analysis of efficacy and 16 patients had partial data excluded from efficacy analysis because of protocol deviations, drug interventions or other factors.

Partial Exclusion of Efficacy Data: A number of efficacy patients had part of their efficacy data excluded because of protocol deviations or other factors such as medical interventions, that affected the efficacy analysis. Sixteen "efficacy" patients had portions of their heart rate and blood pressure data excluded for these reasons. A schematic display of the data included for efficacy analysis is shown in Figure 1 and additional details are provided in Appendix 3.

II Study Results

A. Baseline Demographics and Comparability of Treatment Groups: As can be seen from Tables 3A, 3B and 4 there were no significant differences between the treatment groups with respect to demographic, prestudy clinical and stress EKG data.

B. Efficacy Results: Efficacy results for the primary variables can be seen in Tables 5A, 5B, 6, 7 and 10 ("all" patient analysis). In addition, Tables 12 and 14 display the data for the supplemental anesthesia. In addition, Figures 2-11 complement the above tables. In addition, Tables 12-17 provide information on hemodynamic safety variables and will be discussed under safety.

i) Incidence of Myocardial Ischemia: The occurrence of ST segment shifts and PVCs are summarized by events in Tables 5A and 5B. All patients (n=30) were used for these analysis. Ischemia by EKG was defined in the study protocol as ST segment depression or elevation no greater than 1 mm. When this definition was used five patients (114, 115, 118, 127 and 130) in the placebo group and two patients (128 and 131) in the esmolol group developed ischemia during the study. The study periods during which these ischemic episodes were observed are shown in Table 5A. Clinical data and other details for each of these seven patients are given in Appendix 5. However when the above Holter data were blindly re-evaluated by a independent cardiologist using a similar criteria to that specified in the protocol, the cardiologist found three patients (118, 127 and 130 in the placebo group) and one patient (128 in the esmolol group) with ischemia. Hence no significant difference was detected between the treatment groups and the incidence of ischemic episodes in either the initial evaluation or the re-evaluation. Although the incidence of arrhythmias was not considered a primary efficacy variable the sponsor has analyzed the data in such a manner. However, except for aorta dissection, there were no significant differences between the treatment groups with respect to the proportion of patients who had PVCs at each event.

ii) Maximum Change in Heart Rate and Systolic Blood Pressure: The maximum changes from baseline by study event for heart rate and systolic blood pressure are provided in Table 6 and these are data are graphically displayed in Figures 2-5. There were no significant differences in maximum heart rate change between the groups at any event.

Systolic Blood Pressure: As shown in Table 6, there was a significant difference between the treatment groups for maximum systolic blood pressure change at sternotomy with a change for the esmolol group of -16 mmHg compared to a change for the placebo group of 4 mmHg.

iii) Secondary efficacy variables as shown in Table 7; the average maximum change in rate pressure product at aortic dissection for the esmolol group -.7 was significantly different from that of the placebo group 0.8. However, the actual RPP at aortic dissection reflects values of 7.4 vs 7.8 for the esmolol and placebo group respectively and therefore represent changes that probably have very little clinical meaning.

iv) Results of analysis for maximum changes from baseline for heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and rate pressure product by event for all patients are provided in Tables 10 and 11. Basically, the results of the analysis of the "all" patient group vs the "efficacy" patient group generally show the same trends as previously described.

v) Isoflurane intervention when the MAC unit dose of isoflurane was analyzed by study event. No significant differences were found between the esmolol and placebo groups for any event, although the placebo group received greater amount of isoflurane than did the esmolol group at sternotomy.

III Safety

Adverse Effects: Four patients treated with esmolol (27%) and three patients treated with placebo (20%) exhibited adverse effects during the study. All adverse effects pertained to the cardiovascular system and the most frequently observed adverse effect was hypotension. Hypotension as judged by the investigator, developed in four esmolol patients and in three placebo patients. Two other adverse effects were reported and these occurred with hypotension, atrial fibrillation in one esmolol patient and myocardial ischemia in one placebo patient. The study drug infusion was not discontinued prematurely due to adverse effects in any of these seven patients. These adverse effects are listed in Table 16 along with their severity, onset period, dose duration, treatment group and action taken and outcome.

Hemodynamic Safety Variables: Except for systemic vascular resistance at preinduction, there were no significant differences between the esmolol and placebo groups with respect to the pulmonary capillary wedge pressure, cardiac index and systemic vascular resistance. However, it should be pointed out that cardiac index was consistently lower in the esmolol treated patients during the course of the study. Results of the hemodynamic variables can be seen in Figures 12-17. As shown in Table 21 there appears to be no significant difference in the number of patients with hemodynamic values beyond the safety checkpoints.

IV Analysis and Comments on Study 56

Although there was a reported significant difference at sternotomy, i.e., maximum change in systolic blood pressure between the two treatment groups, one has to question whether this change is clinically significant. It is dubious whether an increase of 4 mmHg (which occurs in the placebo group) would be a sufficient pertubation to increase the risk of myocardial injury. This is very similar to the situation in study 27 in which there was a reported significant difference between the two treatment groups with respect to the maximum change in heart rate response at aortic dissection. Using similar logic, it is not obvious that an increase in heart rate of 8 bpm (in the placebo group) would be a sufficient change to increase the risk of myocardial injury. Hence, other than this one single efficacy parameter, namely systolic blood pressure at sternotomy, there is no apparent statistically significant beneficial pharmacological effect of esmolol in this study. Regarding safety issues, there were no significant differences in the incidence of myocardial ischemia in the two treatment groups. In this setting, there was no increase in the incidence of myocardial ischemia in esmolol treated patients as was seen in the carotid artery study.

D. Issues Raised by the Additional CABG Studies

1. Different Pharmacodynamic Effects with Fentanyl: The effect of esmolol on hemodynamic (heart rate and systolic blood pressure) changes induced by surgical stimuli appears to be modified both qualitatively and quanitatively by IV Fentanyl when compared to the previous studies 51A, 51B, and 49 which used general inhalational agents. In the two CABG studies using IV Fentanyl, esmolol exerted an effect on systolic blood pressure at sternotomy (study 56) and on heart rate at intubation or aortic dissection (study 27). In addition, the pharmacodynamic effects attributable to esmolol i.e., the change in systolic blood pressure at sternotomy and heart rate at aortic dissection (are probably not clinically significant). Moreover, these perioperative studies did not show consistent or parallel pharmacodynamic effects since two different hemodynamic variables were influenced and at different surgical stimuli. In contrast, the perioperative studies which employed esmolol in combination with general inhalation agents (halothane or isoflurane) showed that esmolol exerted its pharmacological effect on blunting both the increase in heart rate and systolic blood pressure following endotracheal intubation. Whether this same blunting effect would have been observed during other surgical stimuli such as skin incision, carotid dissection/cannulation is not known since these endpoints were not evaluated. The overall impression from these studies is that the pharmacodynamics of esmolol when used in combination with Fentanyl may be significantly different than when esmolol is used in combination with general inhalational agents. In general there tends to be a flattening of the overall hemodynamic response and blunting of sympathetic activity with respect to systolic blood pressure and heart rate in the presence of IV Fentanyl which may obscure any additional effect of the esmolol.

2. Differences in Ischemic Events: The results of the two CABG studies also suggest differences in the occurrence of myocardial ischemia compared to study 49 (carotid endarterectomy). The summary table below depicts the overall findings. In both CABG studies the incidence of ischemia was low and there was no statistically significant difference in relative incidence of ischemia between the two treatment groups. There also appeared to be no significant difference in so called "surgical outcomes" (difficulty in weaning patients off cardiac by-pass in the two treatment groups. Hence there appears to be neither an increased risk nor increased benefit from esmolol regarding the incidence of myocardial injury in the CABG studies. In addition, there is reason to believe the incidence of myocardial ischemia may have been underestimated in the two CABG studies. As has been previously mentioned the criteria for ischemia was different (study 27 1mm ST segment Δ greater than 1 min; study 1 mm ST Δ segment Δ greater than 10 seconds). Moreover, there is question re the optimal nature of a single EKG lead (II or V5) to document myocardial ischemia. In this latter regard Slogoff and Keats using two standard leads (II and V5) detected an overall incidence of nearly 40% during the perioperative period in 1023 CABG patients. Of course the extremely low incidence of ischemia in the two CABG studies may further reflect

differences in patient selection, anesthiologists, and anesthetic techniques (IV fentanyl vs thiopental and inhalational agents). Although the two CABG studies do test the hypothesis re a potential adverse effect of esmolol on the incidence of myocaridal ischemia (inferred from the carotid study) translation of the CABG data directly to the carotid artery study is somewhat tenuous. Some of this difficulty arises from major differences in (1) the anesthetic regimens employed; (2) the patient study population (cohorts) and (3) dose and duration of esmolol. There is reason to believe that the carotid artery cohort represented older patients with more advanced ASA class, more hypertension, concomitant CAD and carotid artery disease, etc.

3. Pharmacologic vs Clinical Endpoints: These results further point up an inherent problem pervading all the perioperative studies in this NDA namely none of these studies are measuring hard endpoints. The endpoints are strictly pharmacologic hemodynamic parameters (HR and SBP) and the amount of supplemental anesthesia required. Thus we still do not have conclusive and prospective evidence that esmolol when used in the perioperative setting can significantly influence the incidence of myocardial ischemia/injury which is the primary rationale for employing this intervention. The perioperative studies do provide evidence that esmolol can significantly attenuate two hemodynamic parameters related to ischemia ie tachycardia and RPP. This data combined with intuition and extrapolation from the BHAT type trials with oral beta blockers suggest that beta blockade should be effective in the perioperative setting. Another important aspect of the perioperative studies is the suggestive evidence that the effects of esmolol on hemodynamic parameters (HR and SBP) at various surgical stimuli which are known to release catecholamines may be significantly altered both qualitatively and quantitatively as a function of the anesthetic agent with which it is used, i.e., differences between IV fentanyl and inhalational agents. This latter hypothesis might be worth exploring.

Ronald Lieberman, M.D.

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Orig.
HFN-110
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HFN-110/RLieberman;3/11/86
sb/3/6/86;3/11/86/2923s

SUMMARY TABLE OF PIVOTAL PERIOPERATIVE STUDIES AND CABG STUDIES

Study #	Patient Population	IV Induction-Time	Inhalation Agent	[Esmolol] (Dose/Duration)	Concurrent Meds (β Blocker, Ca^{++} Blocker	Results (Stat Signific)	[Myocardial Ischemia] E	PBO	STD*	Hypotension E	PBO
51A	Gen Surgery	Thiopental 4 mg/kg Min 5	Halothane (0-1.6%)	500X4'-300 X8'(12')	NO	↓HR↓SBP at Intubation					
51B	Gen Surgery	Thiopental 5 mg/kg Min 10	Halothane (0-1.6%)	500X4'-300 X8'(15')	NO	↓HR↓SBP at Intubation					
49	Carotid Artery	Thiopental 6 mg/kg Min 5	Isoflurane (0-6%)	500X4'-300 X8'(12')	NO	↓HR↓SBP at Intubation	5/32	0/30		5/32	5/30
27	CABG	Fentanyl 50 mcg/kg Min 5 or Valium .5 mg/kg	Halothane or Enflurane	500X2'-200-CPB	NO (YES for STD)	↓HR at Intubation ↓HR at aortic dissection ↓use of anesthesia	2/43	4/41	4/18*	2/43	0/41
56	CABG	Fentanyl 40 mcg/kg Min 10 Fentanyl .4 mcg/kg	Isoflurane	500X4'-300-CPB	YES	↓SBP at Sternotomy No difference in Ischemia	1/15	3/15		4/15	3/15

APPENDIX I WILL BE ADDRESSED BY ANOTHER DIVISION WITHIN THE AGENCY

Appendix 2A - Sponsor's Summary of Evidence for Each Claim

E.8. Overall Results and Conclusions

d. Effectiveness

i. Summary of Evidence for Each Claim

Supraventricular Tachycardia

In a double-blind, partial cross-over study (8052-81-05), Brevibloc®, in doses ranging from 50 to 200 mcg/kg/min was found to be significantly effective compared to placebo in reducing the heart rate in patients with SVT. Among the Brevibloc-treated patients 64% responded, while among the placebo-treated patients 8% responded to treatment. The average effective dose of Brevibloc among responders (≥20% reduction in heart rate, heart rate decreased to <100 bpm or conversion to normal sinus rhythm: NSR) was 97.5 mcg/kg/min. In 3% of the patients, SVT was converted to NSR. Therapeutic response rates were similar among patients with atrial fibrillation and atrial flutter. Among patients treated with Brevibloc, postoperative patients had higher therapeutic response rates than non postoperative patients. Therapeutic response rates were similar among patients with ages <65 years and ≥65 years. A rapid reversal (within 30 minutes) of Brevibloc-induced beta blockade was seen after discontinuation of Brevibloc infusion.

In a double-blind, parallel study comparing Brevibloc to intravenous propranolol (Study 8052-81-04), Brevibloc, in the dosage range of 50 to 200 mcg/kg/min, was found to be equally effective to propranolol (3 to 6 mg IV) in reducing heart rate in patients with SVT. Among the Brevibloc-treated patients 72% responded, while 69% of the propranolol-treated patients responded to the treatment. The average effective dose of Brevibloc among responders (≥20% reduction in heart rate, heart rate decreased to <100 bpm, or conversion to NSR) was 115.3 mcg/kg/min. Conversion to NSR was similar in patients treated with Brevibloc (14%) and propranolol (16%). Therapeutic response rates were similar among patients with atrial fibrillation or atrial flutter, patients with ages <65 yrs and ≥65 yrs and between postoperative and non postoperative patients. Significant reversal of Brevibloc-induced beta blockade was seen within 20 minutes after discontinuation of Brevibloc.

In a base line-controlled, open-label study (8052-83-23), in which SVT patients were administered Brevibloc for up to 24 to 48 hours, the drug was found to be effective (either a >15% reduction in heart rate or a conversion to NSR) at a dosage as low as 25 mcg/kg/min. The overall therapeutic response rate was 79%, similar to that observed in the previous two studies. The average effective dosage among responders was 97.2 mcg/kg/min. In 18% of the patients, SVT was converted to NSR. Therapeutic response rates were similar among patients with ages <65 years and ≥65 years; and between postoperative and non postoperative patients. Reversal of heart rate reduction after discontinuation of Brevibloc had no relationship to the length of infusion. Therapeutic response was similar among patients with atrial fibrillation, atrial flutter or sinus tachycardia.

In a second, base line-controlled, open-label study (8052-83-31), Brevibloc was found to be effective (either a ≥15% reduction in heart rate, or a conversion to NSR) in the dosage range of 25 to 150 mcg/kg/min in the treatment of patients with SVT. The overall therapeutic response rate was 78%. The average effective dose among these responders was 61.8 mcg/kg/min. In 14% of the patients, SVT was converted to NSR.

The following table summarizes the response rates in the two well controlled and two partially controlled studies. Overall the response rate was 74% with 71% responding at dosages of 200 mcg/kg/min or less. A dosage-response relationship is also demonstrated over the ranges of ≤ 50 mcg/kg/min to 200 mcg/kg/min.

Management of Perioperative Tachycardia and Hypertension Induced by Endotracheal Intubation

In a double-blind, parallel study (8052-84-51A) the effects of Brevibloc, at a dosage of 300 mcg/kg/min, were compared to placebo on the intubation-induced increases in heart rate and blood pressure among patients with American Society of Anesthesiologists (ASA) physical status classification I or II undergoing surgery. Brevibloc significantly attenuated the increases in heart rate (HR) and systolic blood pressure (SBP) when compared to placebo during the stimulus of endotracheal intubation. The average maximum increases among placebo-treated patients were 38 bpm in HR and 40 mm Hg in SBP, as opposed to an average increase of 23 bpm in HR and 26 mm Hg in SBP in patients treated with Brevibloc. Also, the increases in mean arterial pressure (MAP) and rate-pressure product (RPP) during intubation were significantly lower in Brevibloc-treated patients than in placebo-treated patients. A significantly higher percentage of placebo-treated patients demonstrated a HR ≥100 bpm (42%) and a SBP ≥180 mm Hg (16%) when compared to the Brevibloc treated patients (17% and 8%, respectively).

In a second, double-blind, parallel study (8052-84-51B) comparing Brevibloc (300 mcg/kg/min) with placebo among patients with ASA physical status classification III or IV undergoing surgery, it was found that Brevibloc significantly attenuated the intubation-induced increases in HR and SBP when compared to placebo. The average maximum increases in HR were 24 bpm and 46 mm Hg in SBP among placebo treated patients as opposed to an average increase of 8 bpm in HR and 19 mm Hg in SBP in patients treated with Brevibloc. Also, the increases in MAP and RPP during intubation were significantly lower in Brevibloc-treated patients than in placebo-treated patients. A significantly higher percentage of placebo-treated patients (26%) demonstrated HR ≥100 bpm (18%) and SBP ≥180 mm Hg (11%) when compared to the Brevibloc-treated patients (4% and 11%, respectively). There was no significant difference in the response to Brevibloc between patients with age <65 years and ≥65 years.

In a third, double-blind, parallel study (8052-83-49) the effects of Brevibloc in comparison to those of placebo were evaluated on the endotracheal intubation-induced increases in HR and SBP among patients undergoing carotid endarterectomy. Brevibloc significantly attenuated the intubation-induced increases in HR and SBP when compared to placebo. The average maximum increase among placebo-treated patients was 24 bpm in HR and 45 mm Hg in

SBP as opposed to an average increase of 8 bpm in HR and 2 mm Hg in SBP in patients treated with Brevibloc. In addition, the increases in diastolic blood pressure, MAP and RPP during intubation were significantly lower in Brevibloc-treated patients when compared to placebo-treated patients. A significantly higher percentage of placebo-treated patients demonstrated HR >100 bpm (18%) and SBP >180 mm Hg (26%) as opposed to Brevibloc-treated patients (1% and 18%, respectively).

Thus, Brevibloc was shown to be effective in management of the tachycardia and hypertension known to occur during the endotracheal intubation among anesthetized patients undergoing surgery. A summary of these three studies and the overall results are provided in the following three figures (HR change, SBP change, and RPP change). Since the study designs for all three studies were virtually the same, the data from all three studies were also pooled for this overall evaluation.

2B

Appendix 2B - Esmolol Conversion Rate from SVT to NSR

EFFICACY PATIENTS IN WHOM SVT WAS INITIALLY CONVERTED TO NSR

Study #8052-81-04

Titration Period

Esmolol (14%) N=50

Pt.#	Type of SVT
610	A-FIB
809	A-FIB
821	A-FIB
911	A-FL
1502	AFIB
1506	AAT
1520	A-FIB

Propranolol (16%) N=55

Pt.#	Type of SVT
607	A-FIB
612	A-FIB
817	A-FIB
824	A-FIB
925	A-FIB
1403	ST.
1408	A-FIB
1509	A-FIB
1511	A-FIB

Maintenance Period

Esmolol (10%) N=30

Pt.#	Type of SVT
825	A-FIB
1516	A-FIB
1518	A-FL

Propranolol (8%) N=36

Pt.#	Type of SVT
931	A-FIB
1308	A-FIB
1522	A-FIB

Overall, in 10 patients (20%) treated with esmolol (N=50) and in 12 patients (22%) treated with propranolol (N=55) SVT was converted to NSR.

Study #8052-81-05

Initial Titration Period

Esmolol (6%) N=32

Pt.#	Type of SVT
208	A-FL
903	A-FIB

No patient in the placebo group was converted to NSR.

Study #8052-83-23,30,36

Titration Period

Esmolol (4%) N=147

Pt.#	Type of SVT
01-01	PSVT
09-03	A-FIB
18-01	PSVT
21-01	A-FL
21-04	A-FIB
30-01	A-FIB

Maintenance Period

Esmolol

Pt.#	Type of SVT
05-01	A-FIB
05-05	A-FIB
05-20	A-FIB
06-02	A-FL

Pt.#	Type of SVT
06-03	A-FIB
08-01	A-FIB
08-04	A-FIB
08-08	A-FIB
09-02	A-FL
09-07	A-FL
12-02	A-FL
14-02	A-FIB
17-01	A-FIB
18-08	A-FIB
18-11	A-FIB
21-02	A-FL
21-03	A-FIB
21-06	PSVT
21-07	A-FIB
21-08	A-FL
22-06	A-FL
30-04	A-FIB
30-06	A-FL

Overall, in 29 patients (20%) treated with esmolol (N=147), SVT was converted to NSR.

Study #8052-83-31

Titration Period

Esmolol (5%) N=58

Pt.#	Type of SVT
07-06	MAT
10-02	A-FIB
10-09	A-FIB

Maintenance Period

Esmolol

Pt.#	Type of SVT
03-02	A-FIB
05-01	A-FL
05-02	A-FIB
05-08	A-FIB
08-03	A-FL

Overall, in eight patients (14%) treated with esmolol (N=58) SVT was converted to NSR.

A-FIB = ATRIAL FIBRILLATION

A-FL = ATRIAL FLUTTER

AAT = AUTOMATIC ATRIAL TACHYCARDIA

ST = SINUS TACHYCARDIA

PSVT = PAROXYSMAL SUPRA VENTRICULAR TACHYCARDIA

MAT = MULTIFOCAL ATRIAL TACHYCARDIA

2C

Appendix 2C - ADE by Body System in SVT and Perioperative Studies

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	180	77	383	44	63
CARDIOVASCULAR***											
Bradycardia	0	2	0	0	0	0	1	1	2	0	2
Decreased Heart Rate	0	0	1	0	0	0	0	0	1	0	0
ECG Abnormality (NOS)	0	0	0	0	0	0	0	1	1	0	0
Heart Block	0	0	0	0	0	0	0	1	1	0	0
Increased VPC's	0	0	1	0	0	0	0	0	1	0	0
Junctional Rhythm	0	0	1	0	0	0	0	0	1	0	0
Paired VPC's	0	0	1	0	0	0	0	0	1	0	0
Premature Ventricular Contraction	1	0	0	0	0	0	0	0	1	0	0
S V Tachycardia	0	0	0	0	0	0	2	0	2	0	0
Ventricular Arrhythmia	0	0	0	0	0	0	1	0	1	0	0
Ventricular Ectopy	0	0	0	0	0	0	0	1	1	0	0
Hypotension (symptomatic)	23 (4)	4 (1)	8 (7)	1 (1)	0	1 (1)	70 (21)	35 (11)	137(44)	1 (1)	4 (1)
Increased Congestive Heart Failure	0	1	0	0	0	0	0	0	0	0	1
Increased Pulmonary Artery Pressure	0	0	1	0	0	0	1	0	2	0	0
Narrowed Pulse Pressure	0	0	0	0	0	0	2	0	2	0	0
Peripheral Ischemia	0	0	0	0	0	0	3	1	4	0	0
Angina	0	0	0	0	0	0	1	0	1	0	0
Chest Pain	0	0	0	1	0	0	1	2	3	1	0
Diaphoresis	4	0	7	0	0	2	18	8	37	0	0
Dyspnea	0	0	1	0	0	0	2	0	3	0	0
Flushing	0	0	0	0	0	0	2	0	2	0	0
Pallor	0	0	0	0	0	0	2	0	2	0	0
Shortness of Breath with Dyspnea	1	0	0	0	0	0	0	0	1	0	0
Syncope	0	0	0	0	0	0	0	1	1	0	0
Number of Patients Experiencing a Cardiovascular Adverse Reaction	28	8	12	1	0	3	81	38	158	1	6
Percentage of Patients Experiencing a Cardiovascular Adverse Reaction	41%	10%	18%	2%	0%	25%	51%	41%	41%	2%	10%

* Includes 32 placebo patients who were crossed-over to esmolol
** Includes 9 esmolol patients who were crossed-over to placebo
*** Cardiovascular adverse reactions have been grouped according to ECG abnormality, signs and symptoms