Re 58/43

1. Percent beta blockade vs log dose (esmolol)

2. Log percent blockade vs time after stopping the infusion for 50, 100, 200 and 300 mcg/kg/min

3. Percent blockade vs log blood concentration

4. Time course of beta blockade for entire study period (#2)

5. If possible pool percent blockade vs log blood for the I_{25} starting at lowest dose (This turned out not to be feasible)

Re 03

1. Log blood conc vs time (esmolol and acid metabolite)

2. Log percent blockade vs time

The results of the above requested data will be presented in the Addendum for Clinical Pharmacology.

II) Preliminary Analysis and Comment

The results of studies 58 and 43 clearly showed beta blockade in man. The isoproterenol (I_{25}) dose ratios imply that 7 times more I_{25} is required to achieve the I_{25} at Brevibloc doses of 750 compared to 100 mcg/kg/min. It is not clear how to compare the relative potency of esmolol and propranolol. There appears to be a contradiction in the dose response curve for Study 58 vs study 43.

Study 43 (based on I_{25} dose ratios suggest that esmolol doses of 300 are not at the top of the curve while data from study 58 suggest that the 300 dose is at the top or plateau of the curve (since there is no real difference between doses of 100, 200 or 300 mcg/kg/min. This is of interest since the results of the SVT controlled trials suggest that a dose response effect is seen at each stepwise increment thru 200 (and that most of the clinical response is achieved by 150 mcg/kg/min. One possible explanation for the inconsistency is that I_{25} inhibition may not be a good predictor of clinical response in SVT (control of heart rate). See Addendum for further analysis of the new data.

Study 8052-84-58

Study Objective

The objective was to determ the relationship between duration of esmolol infusion and onset and degree of beta blockade, at 3 dose levels. A secondary purpose was to examine the relationship between esmolol blood levels and beta blockade during infusion and after discontinuation.

Study Design and Treatment Plan

The study was a single blind, placebo baseline controlled study involving 12 healthy male subjects who were selected by the investigator from the local population. All subjects remained hospitalized during the entire study duration. Esmolol was given in two phases, first a loading infusion of 500 mcg/kg/min was administered for 1 to 1 1/2 minutes and followed by maintenance infusions of either 100, 200, and 300 mcg/kg/min for a total duration of 16 minutes.

Test Parameters for Safety/Efficacy

The level of beta blockade was assessed by determining heart rate responses to bolus IV injections of isoproterenol prior to, during and after termination of esmolol infusion.

Results

A more detailed display of the data is presented in the Addendum to the Clinical Pharmacology.

1) Consistent with its activity as a beta adrenergic receptor antagonist, esmolol reduced the heart rate response to isuprel. This beta blocking effect was rapid in onset (within 5 minutes after initiation of the loading infusion) and rapid in offset (4% beta blockade at 45 minutes following termination of the maintenance infusion). At each dose level studied, the degree of beta blockade was not significantly different over a 55 minute period. Although the level of beta blockade tended to increase with dose; however this effect was neither dramatic nor statistically significant (p equals 0.10). Overall means (combined 5, 10, 30 and 55 minute data) for percent beta blockade at each of the maintenance infusion rate were 50% at 100 mcg/kg/min, 57% at 200 mcg/kg/min and 65% at 300 mcg/kg/min. The relatively shallow dose response curve and low level of maximal beta blockade produced by esmolol may relate to the relative cardioselective nature of the drug; i.e., esmolol would not be expected to significantly block the part of the isuprel induced increase in heart rate mediated by reflex vagal withdraw due to peripheral vasodilation.

2) In addition, the level of beta blockade was directly related to blood concentration of esmolol but not blood levels of the acid metabolite, ASL-8123. Blood levels of esmolol were relatively stable at 5, 10, 30 and 55 minutes during each of the esmolol maintenance infusions (see Table below). However, blood levels of esmolol decreased rapidly following termination of the 300 mcg/kg/min infusion. Blood levels of the acid metabolite of esmolol increased with time during all infusions. During the 45 minute period following termination of esmolol infusion, however, the levels remained virtually unchanged (38.00 to 38.97 mcg/ml).

Blood Levels of Esmolol and Its Acid Metabolite (ASL-8123)

Maintenance Dose (mcg/kg/min)	Time (min)	Esmolol Concentration* (mcg/ml)	Mean Comparisons	Metabolite Concentration* (mcg/ml)	Mean Comparisons
100	5	0.31±0.04	55>30>10,5	0.18±0.16	55>20>10>5
	10	0.32±0.04		0.67±0.29	
	30	0.44±0.04		3.33±0.21	
	55	0.52±0.05		6.40±0.2[illegible]	
200	5	0.94±0.13	N.S.	7.20±0.31	55>30>10>5
	10	0.99±0.09		8.23±0.30	
	30	1.05±0.10		12.74±0.35	
	55	1.11±0.11		18.38±0.46	
300	5	1.69±0.21	N.S.	20.72±0.70	55>30>10>5
	10	1.64±0.19		22.31±0.69	
	30	1.61±0.22		27.61±0.54	
	55	1.71±0.21		33.62±0.66	
Follow-up	5	0.43±0.09	5>10>30,45	38.71±1.48	N.S.
	10	0.17±0.03		38.00±0.90	
	30	0.03±0.00		38.97±1.16	
	45	0.02±0.00		38.62±1.14	

Values are mean ± S.E.M.

* Concentrations are expressed as the hydrochloride salt.

Adverse Effects

The sponsor reported that adverse effects occurred in only one subject treated with esmolol. This subject experienced dizziness twice: once during each loading dose. Each episode of dizziness persisted for around 5 minutes, was moderate in severity and resolved without intervention. This patient also showed an increase in PVC frequency which was present for 2 hours during the course of the 100 and 200 mcg/kg/min maintenance infusions. In addition, there were minor instances of bradycardia and hypotension. These appeared to be transient in nature and were quickly reversible following termination of esmolol infusion.

Study 8052-83-43

The objective of this study was to compare by measurement of heart rate responses to isuprel the potency and duration of beta blockade produced by IV esmolol vs IV and oral propranolol in healthy adult male volunteers.

Study Design and Treatment Plan

This was an open label randomized placebo baseline controlled study in 14 male volunteers ranging from 21 to 35 years old. Thirteen of these subjects were defined as healthy and one subject had clinically significant elevated white blood count levels. There were three treatment plan schedules which were as follows:

a. Esmolol maintenance doses of 100, 200, 250, 300, 500, and 750 mcg/kg/min for 1 hour each preceeded by a 1-1.5 minute loading infusion of 500 mcg/kg/min.

b. Propranolol 55 mcg/min for 1 hour with a loading dose of 10 mg (administered at a rate of 1.1 mcg/min).

c. Oral propranolol 40 mg/tid X 4 days then 80 mg/tid X 2 days and then 10, 20, and 40 mg q 8 hours X 2 days.

Test Parameters for Safety/Efficacy

Measurement of heart rate response to isoproterenol challenge during each dosing regimen. The I_{25i} doses of isoproterenol required to increase heart rate by 25 bpm (I25i) were determined by 2 different methods: during each IV infusion of esmolol or propranolol, the I25 was estimated (I25e) so that this dose could be administered during subsequent infusions or after termination of beta blocker infusion. Also following completion of the study, I25 doses were calculated by linear regression analysis and interpolation (I125i). Isoproterenol dose ratios were calculated as the I_{25i} determined during beta blocker administration divided by the I25i obtained during placebo infusion (control).

Results

Isoproterenol (I_{25i}) dose ratios (mean ± S.E.M.) for the various doses of Brevibloc and propranolol were as follows:

Brevi-	100 mcg/kg/min	2.00±0.09	Propranolol	10 mg	9.12±0.85
bloc	200	2.38±0.15		20	18.42±1.46
	250	3.58±0.29		40	33.50±3.32
	300	3.80±0.24			
	500	10.06±1.69		IV	33.09±2.26
	750	15.25±0.99			

As can be seen from the above summary table, I_{25} dose ratios obtained with propranolol were considerably higher than those obtained with esmolol. In addition, the effect of 500 mcg/kg/min of esmolol was approximately equal to an oral dose of propranolol of 10 mg q 8 hours. Again as was observed in the preceeding study (8052-84-58) beta blockade produced by esmolol resulted in a shallow dose response curve and low level of maximal beta blockade. Esmolol produced stable levels of beta blockade within 5 minutes of each maintenance infusion (preceded by loading dose). Recovery from beta blockade was relatively quick following termination of the esmolol infusion (300 mcg/kg/min). Eighteen minutes post termination of the infusion, the heart rate response to the control I25e was 25 bpm and blood levels of esmolol were negilible (note at this time the mean biood level of the acid metabolite of esmolol was 35 mcg/m/L). In contrast, at 14-28 minutes after termination of the IV propranolol infusion, the heart rate responses to the control I25e were modest and not significantly different from each other (2 bpm and 4 bpm respectively). Blood levels of propranolol als; were not significantly different at these two times.

Adverse Effects

8 (57%) of the 14 study subjects exhibited some form of adverse reaction (headache, nausea, vomiting, diarrhea, arrhythmia, and hypotension). In all, 12 adverse effects occurred. Headache was the most frequent adverse effect and occurred in 6 subjects treated with esmolol. In the 5 of the 6 subjects headache was associated with the 750 mcg/kg/min infusion of esmolol. Hypotension 90/60 occurred in one subject during the infusion of esmolol at 500 mcg/kg/min. Hypotension resolved within 40 minutes after stopping the infusion. In conclusion, IV esmolol was much less effective than IV or oral propranolol in attenuating the heart rate response to isoproterenol. The 500 mcg/kg/min dose of esmolol produced a similar effect to that of an oral dose of 10 mg q 8 hours of propranolol. According to this study model, evaluation of the beta blocking activity of esmolol compared to propranolol was complicated due to (1) Brevibic being a beta 1 selective blocker whereas propranolol is not and (2) high doses of esmolol increased baseline (preisuprel) heart rate. Since the level of beta blockade was similar at 5 and 25 minutes during each of the esmolol maintenance infusions, it is apparent that steady state levels of beta blockade are rapidly obtained. In addition, recovery from beta blockade was rapid (18 minutes after termination of esmolol). The results are consistent with a time dependent recovery from beta blockade following termination of the esmolol infusion whereas there was little time dependent recovery from beta blockade with propranolol.

Analysis and Comment

In both study 58 and 43 steady state levels of esmolol were rapidly attained and proportional to dose. The level of beta blockade was not significantly different during the length of the maintenance infusion periods in these studies. Moreover, offset of beta blockade was rapid following termination of the maintenance infusion. While the data supports that esmolol is a true beta blocker in man, its relative potency re propranolol is not readily apparent nor is the dose response effect on inhibition of isoproterenol.

Study 8052-81-03

This was a tolerance study in which both pharmacokinetics and pharmacodynamics were also evaluated.

Study Objectives

1. To evaluate the effect of varying the duration of esmolol infusion (150 mcg/kg/min) from 6 to 48 hours upon blood levels of esmolol and the major metabolite (ASL 8123) during and after the infusion.

2. To evaluate the relationship between esmolol ASL 8123 blood levels during and after infusing esmolol at 150 mcg/kg/min for durations ranging from 6 to 48 hours.

3. To evaluate the relationship between blood levels of esmolol, ASL 8123, the attenuation of maximal isoproterenol-induced increases in heart rate and percent beta blockade during and after infusing esmolol at 150 mcg/kg/min for 6-48 hours.

Patient Selection and Treatment Plan

The subjects were infused with esmolol for durations of 6 hours (Group I, n=1), 12 hours (Group II, n=1), 24 hours (Group III, n=1), 36 hours (Group IV, n=2), and 48 hours (Group V, n=6). In addition, the mean blood levels of esmolol and metabolites for all patients combined were also provided at each time interval.

Study Results

a. The following table illustrates the fact that the mean esmolol blood concentrations remained more or less constant at all measurement times during the infusion (5-44 hours). In contrast, however, blood concentrations of ASL 8123 showed a progressive increase from 5-16 hours and thereafter demonstrated a plateau up to 44 hours.

Table

Summary of Esmolol and ASL 8123 Blood Concentrations During Esmolol Infusion

Patient Group (Esmolol vs. ASL 8123)	Hour 6 (Mean±SEM)	Hour 11 (Mean±SEM)	Hour 18 (Mean±SEM)	Hour 23 (Mean±SEM)	DURING INFUSION Hour 28 (Mean±SEM)	Hour 33 (Mean±SEM)	Hour 38.5 (Mean±SEM)	Hour 44 (Mean±SEM)
Group 1 (N=1)								
Esmolol (mcg/mL)	0.62	NA	NA	NA	NA	NA	NA	NA
ASL 8123 (mg/mL)	32.4							
Group 2 (N=1)								
Esmolol (mcg/mL)	0.66	0.78	NA	NA	NA	NA	NA	NA
ASL 8123 (mcg/mL)	37.8	56.5						
Group 3 (N=1)								
Esmolol (mcg/mL)	0.46	0.31	0.27	0.21	NA	NA	NA	NA
ASL 8123 (mcg/mL)	48.4	68.7	73.0	75.0				
Group 4 (N=2)								
Esmolol (mcg/mL)	1.11±0.52	1.18±0.23	0.88±0.44	0.73±0.46	0.88±0.43	0.98±0.44	NA	NA
ASL 8123 (mcg/mL)	47.4±3.0	63.9±0.9	71.7±1.0	74.1±1.8	71.9±1.2	71.6±2.0		
Group 5 (N=9)								
Esmolol (mcg/mL)	0.80±0.12	0.81±0.20	0.78±0.29	0.82±0.31	0.59±0.11	0.77±0.16	0.88±0.19	0.89±0.19
ASL 8123 (mcg/mL)	38.0±2.4	56.0±2.4	64.0±3.7	68.5±3.9	67.4±4.5	62.0±4.5	69.0±4.0	66.0±4.0
All Patients								
Esmolol (mcg/mL)	0.80±0.11 (N=11)	0.71±0.15 (N=10)	0.75±0.18 (N=9)	0.54±0.12 (N=9)	0.61±0.12 (N=8)	0.81±0.15 (N=8)	0.88±0.18 (N=8)	0.89±0.19 (N=8)
ASL 8123 (mcg/mL)	40.7±2.0 (N=11)	59.0±1.9 (N=10)	67.4±2.5 (N=9)	68.4±3.9 (N=9)	65.5±3.6 (N=8)	64.6±3.6 (N=8)	69.0±4.0 (N=8)	66.0±4.0 (N=8)

NA Not applicable since blood samples were not obtained at these times.

b. Esmolol had a significant effect on blunting the isoproterenol induced maximum increase in heart rate during the infusion at all time points when compared to the preinfusion period. As is shown in the table below sigificant beta blockade was present at all measurement times during the esmolol infusion. Moreover a significant positive correlation was found between esmolol blood levels and the percent beta blockade.

Table

Summary of Percent Beta Blockade During Esmolol Infusion

Group (Duration of Esmolol Infusion)	DURING INFUSION Hour 8 (Mean±SEM)	Hour 11 (Mean±SEM)	Hour 18 (Mean±SEM)	Hour 23 (Mean±SEM)	Hour 28 (Mean±SEM)	Hour 33 (Mean±SEM)	Hour 38.5 (Mean±SEM)	Hour 44 (Mean±SEM)
Group 1 (6 hours) (N=1)	30.0	NA	NA	NA	NA	NA	NA	NA
Group 2 (12 hours) (N=1)	47.0	47.0	NA	NA	NA	NA	NA	NA
Group 3 (24 hours) (N=1)	50.0	33.3	33.3	50.0	NA	NA	NA	NA
Group 4 (36 hours) (N=2)	50.0± 5.0	25.0± 15.0	35.2± 9.3	37.0± 3.7	31.5± 13.0	27.0± 5.0	NA	NA
Group 5 (48 hours) (N=6)	53.0± 4.6	39.6± 5.5	49.0± 4.8	48.5± 5.9	42.5± 5.4	35.0± 5.7	34.3± 4.9	48.3± 3.2
All Patients	50.3± 3.9 (N=11)	37.1± 4.4 (N=10)	44.1± 4.8 (N=9)	46.1± 4.2 (N=8)	39.0± 5.0 (N=8)	33.2± 4.5 (N=8)	34.3± 4.9 (N=6)	48.3± 3.2 (N=6)

NA is not applicable.

c. Esmolol blood levels diminished rapidly upon discontinuation of the infusion whereas levels of ASL-8123 were present at significant levels for up to 4 hours following the infusion. A summary of these results is provided in the accompanying table.

Table

Summary of Esmolol and ASL 8123 Blood Concentrations
At End of Esmolol Infusion and Post Esmolol Infusion

Patient Groups Blood Level (Esmolol vs. ASL 8123)	End of Infusion Blood Levels	POSTINFUSION Min 0 (Mean±SEM)	Min 15 (Mean±SEM)	Min 45 (Mean±SEM)	Min 75 (Mean±SEM)	Hour 2 (Mean±SEM)	Hour 4 (Mean±SEM)	Hour 6 (Mean±SEM)
Group 1 (N=1)								
Esmolol (mcg/mL)	0.82	0.19	0.07	•	•	•	•	•
ASL 8123 (mcg/mL)	32.4	39.8	40.4	37.8	33.8	28.8	14.1	•
Group 2 (N=1)								
Esmolol (mcg/mL)	0.78	0.12	0.04	•	•	•	•	•
ASL 8123 (mcg/mL)	58.5	59.5	58.3	52.1	46.3	41.1	24.9	16.7
Group 3 (N=1)								
Esmolol (mcg/mL)	0.21	0.07	0.02	•	•	•	•	•
ASL 8123 (mcg/mL)	75.8	78.7	78.8	78.1	66.4	49.2	36.8	25.3
Group 4 (N=2)								
Esmolol (mcg/mL)	0.88	0.11	0.02	0.02*	•	•	•	•
	0.46	0.02	0.00					
ASL 8123 (mcg/mL)	71.0	73.3	70.5	65.8	61.0	59.3	37.7	26.0
	2.9	2.1	1.8	4.9	4.1	0.8	4.8	4.2
Group 5 (N=6)								
Esmolol (mcg/mL)	0.88	0.11	0.06	0.04	•	•	•	•
	0.19	0.03	0.02	0.02				
ASL 8123 (mcg/mL)	66.8	61.4	57.8	56.2	51.9	44.3	28.8	19.1
	4.8	3.7	5.2	3.9	4.7	4.8	3.1	2.8
All Patients								
Esmolol (mcg/mL)		0.11	0.05	0.03	•	•	•	•
		0.02	0.01	0.01				
		(N=11)	(N=11)	(N=2)				
ASL 8123 (mcg/mL)	NA	52.3	52.3	57.1	52.8	46.7	29.4**	20.8**
		3.4	3.7	3.3	3.8	3.8	2.7	1.9
		(N=11)	(N=11)	(N=11)	(N=11)	(N=11)	(N=11)	(N=10)

* Not at this time interval because blood levels in one patient were not available.
** Significantly lower than other mean postinfusion concentrations of ASL 8123.
\# Not at this time interval because blood levels in the remaining four patients were not available.
NA Is not applicable due to differences in the duration of the infusion among the groups.
• Below quantifiable limits.

d. Finally, the percent of beta blockade was shown to decline rapidly by 16-45 minutes post infusion in all groups infused with esmolol (see accompanying table). At this time (post 16-45 minutes), as shown in the previous table, esmolol blood levels were negligble indicating a significant positive correlation (p less than 0.03) between esmolol blood levels and percent beta blockade. Thus it is interesting to note that a significant decrease in beta blockade at the 16-45 minutes post infusion period is obtained while blood levels of ASL-8123 showed significant persistence for up to 4-6 hours post infusion. Therefore the beta blockade observed in this study was not related to ASL-8123 found in this study.

Table

Summary of Percent Data Displaced At the End of Esmolol Infusion and Post Esmolol Infusion

Group (Duration of Esmolol Infusion)	End of Infusion (Mean±SEM)	Post Infusion Min 0 (Mean±SEM)	Min 10 (Mean±SEM)	Min 45 (Mean±SEM)	Min 75 (Mean±SEM)	Hour 2 (Mean±SEM)	Hour 4 (Mean±SEM)	Hour 6 (Mean±SEM)
Group 1 (6 hours) (N=1)	30.8	30.8	23.1	7.7	15.4	15.4	0	NA
Group 2 (12 hours) (N=1)	47.8	21.7	47.8	30.1	-13.0	21.7	4.3	-13.0
Group 3 (24 hours) (N=1)	30.0	25.0	33.3	8.3	8.3	8.3	-17.0	8.3
Group 4 (36 hours) (N=2)	27.8± 5.6	8.3± 8.3	1.9± 1.9	-1.9± 20.0	5.6± 5.6	-16.0± 19.0	-20.0± 24.0	-13.0± 19.0
Group 5 (48 hours) (N=6)	40.3± 3.2	20.8± 7.3	47.5± 10.9	22.2± 5.6	16.8± 5.6	1.9± 8.8	-7.7± 9.8	9.2± 4.7
All Patients (N=11)	NA	21.8±* 6.5	33.0±* 7.3	15.8± 4.9	9.9± 3.2	7.4±* 5.9	-0.8±* 9.9	-0.2±* 4.8

NA Is not applicable due to differences in the duration of infusion among the groups.
NR Is not retrievable.
* Postinfusion minute 0 and minute 10 were significantly different from postinfusion hours 2, 4 and 6.

ii. Hemodynamic Effects (non-invasive and invasive)

Overview Summary

While the results of the various hemodynamic studies with esmolol do not indicate anything unexpected in terms of its effects on hemodynamic parameters, several points warrant emphasis.

1) In study 15, direct comparison with IV propranolol showed that at peak exercise, SBP was significantly lower with esmolol. This is of considerable interest since in the SVT efficacy trials (study 04 and 05) the overall incidence of hypotension was quite high particularly in the comparative trial with propranolol (study 04).

2) In study 25, each of the key hemodynamic variables showed a dose response effect with increasing doses of esmolol. This suggests two potential problems: (1) in the presence of anesthesia, the dose response curve for these variables may be altered and (2) patients with CAD may be relatively more sensitive to esmolol in the presence of anesthesia. This is of interest since the results of the efficacy trial in perioperative patients with CAD-Study 49 indicated a significant incidence of myocardial ischemia associated with esmolol.

Study 8052-82-15

Objectives

To compare the effects of esmolol and propranolol on left ventricular function at rest and during exercise in patients undergoing radionuclide angiography by the first pass technique.

Study Design and Patients

The study was a double-blind randomized crossover with active control. 15 patients entered and completed the study, 12 of these patients had coronary artery disease.

Treatment Plan and Test Parameters for Safety and/or Efficacy

All patients received both study drugs in a double-blind crossover fashion. Esmolol was given as a 2 minute loading dose of 500 mcg/kg/min followed by a continuous infusion of 200 mcg/kg/min until the time of peak exercise. Propranolol was administered as four 1 mg injections each given over a 1 minute period with a 2 minute observation period between 2nd and 3rd injections. Radionuclide angiography at rest and at peak exercise were determined. Studies were performed predrug, during esmolol and during propranolol, with 48 hour washouts between each.

Study Results

In general, esmolol and propranolol produced a similar hemodynamic profile both at rest and during exercise. Data for five key variables were plotted. See Appendix 1B for details. The following conclusions are supported by this data.

a. At rest the HR, SBP, RPP, left ventricular ejection fraction, right ventricular ejection fraction, cardiac index, and contractility index were significantly lower following either drug when compared to values obtained on control days. Esmolol and propranolol produced a similar increase in left ventricular and systolic volume at rest. No significant differences were detected between esmolol and propranolol for any of the hemodynamic variables at rest.

b. Very similar results were noted at peak exercise, except there was no significant difference between either esmolol or propranolol in the control day values regarding left ventricular ejection fraction, or left ventricular end diastolic volume. At peak exercise, the two drugs differed only with respect to systolic blood pressure - systolic blood pressure was significantly lower at peak exercise with esmolol than with propranolol administration. (This observation is significant since in the controlled clinical trial study 04 the incidence of hypotension was significantly higher in the esmolol group compared to propranolol.)

c. The increases in heart rate, systolic blood pressure and rate pressure product during exercise were significantly less following esmolol or propranolol treatment than the control.

d. After discontinuation of esmolol infusion at peak exercise, heart rate returned to baseline whereas in the same period after stopping propranolol, heart rate remained below the baseline for the entire 30 minute post infusion period.

e. A statistically significant drop in the average esmolol blood level from the steady state level during the infusion to a very low level during the 30 minute post infusion period was noted. This esmolol blood level data was obtained in 9 patients. However, since propranolol blood level data was obtained in only 3 patients, these blood levels were not analyzed statistically.

f. According to the sponsor, no adverse effects were reported by the investigator nor were any adverse hemodynamic effects found in reviewing the hemodynamic data. However, it should be noted as reported under "c" systolic blood pressure was significantly lower at peak exercise with esmolol than with propranolol administration.

In summary esmolol and propranolol in the doses specified resulted in similar decreases in the heart rate, ejection fraction, double product, and cardiac index, both at rest and during exercise in 15 patients undergoing radionuclide angiography.

Study 8052-82-14

Objective

To evaluate the hemodynamic effects of esmolol in patients undergoing cardiac catherization using invasive and angiographic or multiple gated acquisition blood pool imaging techniques.

Study Design and Patients

This was an open label evaluation in 12 patients, 7 of whom had documented coronary artery disease.

Treatment Plan and Test Parameters for Safety and/or Efficacy

A esmolol loading dose of 500 mcg/kg/min for 4 minutes followed by maintenance infusion of 300 mcg/kg/min for a total infusion time of 20-27 minutes. The following hemodynamic measurements were obtained at baseline, minute 14 of the infusion and 30 minutes post infusion: HR, SBP, cardiac index, stroke work index, and left ventricular ejection fraction.

Study Results

1) As can be seen from the accompanying table, esmolol infusion produced a modest but statistically significant reduction in six hemodynamic variables.

heart rate	4 bpm, from base line of 73 bpm
systolic blood pressure	15 mm Hg, from base line of 152 mm Hg
cardiac index	0.5 L/min/m^2, from base line of 2.88 L/min/m^2
stroke volume index	5 mL/beat/m^2, from base line of 40 ml/beat/m^2
stroke work index	10 gm·M·beat/m^2, from base line of 50 gm·M·beat/m^2
left ventricular ejection fraction	14%, from base line of 74%

2) The above data was also plotted in graph form. See Appendix 1B.

3) Other related variables including RPP and cardiac output were also significantly reduced from baseline. However diastolic blood pressure was not significantly changed. Although myocardial contractility (dP/dt) tended to decrease during the infusion, the reduction was not statistically significant from baseline.

4) In contrast to the situation re (ASL-8123) in which blood levels continued to increase through the final sampling time at 30 minutes post infusion, by 30 minutes post infusion, nearly all patients had less than quantifiable levels of esmolol in both arterial and venous blood.

5) At steady state, the mean arterial esmolol blood level (3.91 mcg/ml) was more than seven times higher than the mean venous blood level (0.53 mcg/ml).

Adverse Effects

One of the 12 patients who had severe coronary artery disease and impaired left ventricular function exhibited hypotension at minute 10 of the infusion requiring discontinuation of esmolol. Hypotension lasted a total of 40 minutes and may have been complicated by the administration of other drugs such as nitroglycerin and lasix. According to the sponsor no patient had a systolic blood pressure of less than 90 mm Hg during the esmolol infusion nor had a heart rate less than 50 bpm during the study. Three patients had normal baseline ventricular wall motion that became abnormal during esmolol infusion. Thus the drug potentially could cause abnormalities in left ventricular function or contractility in certain patients. In summary, infusion of esmolol at a dosage of 300 mcg/kg/min produced modest but

statistically significant hemodynamic changes typical of beta adrenergic blockade. Consistent with the short half life of esmolol, hemodynamic effects were quickly reversed upon discontinuation of the esmolol infusion.

Study 8052-83-25

Introduction

Although some of the hemodynamic effects of esmolol have been discussed previously the results reported in this section are presented separately to underscore their importance because they represent a study in anesthetized patients postintubation prior to CABG surgery. The implications of this study in relationship to the perioperative clinical trials of esmolol, particularly in study 49 (carotid artery patients) will also be discussed. In addition, a summary of hemodynamic data in CAD patients will be presented.

Study Objective

To investigate the effects of different doses of esmolol (100, 200, and 300 mcg/kg/min) vs placebo on safety and systemic hemodynamics in patients anesthetized with fentanyl, oxygen and pancuronium prior to CABG surgery.

Study Design and Patients

This double-blind, randomized, placebo controlled trial enrolled 20 patients with documented coronary artery disease. Ten patients received esmolol and ten received placebo. Hemodynamic data from 2 placebo patients were excluded because one patient received an excluded drug (nifedipine) prior to the study and one patient received a vasodilator (IV nitroglycerin).

Treatment Plan and Test Parameters for Safety And/Or Efficacy

After induction of anesthesia and endotracheal intubation, esmolol or placebo was infused I.V. for a maximum of 34.5 minutes. The esmolol infusion rate was increased in a stepwise fashion from 100 mcg/kg/min to 200 and finally to 300 mcg/kg/min; each dose was given for 10 minutes and each was preceeded by a loading dose of 500 mcg/kg/min for 1.5 minutes. Hemodynamic measurements including pulmonary artery catheter measurements were taken prior to induction after intubation, at the end of each dose level of infusion and at 15 and 30 minutes post infusion. Predefined hemodynamic safety checks were established and if any one of these was reached the study drug was suppose to be discontinued. These included: 1) SBP less than 90 mm Hg; 2) DBP less than 50 mm Hg; 3) HR less than 50 bpm; 4) CI less than 2.0 L/min/m^2; 5) PCWP greater than 20 mm Hg. The following measured hemodynamic variables were analyzed:

1. Heart rate
2. Systolic blood pressure
3. Diastolic blood pressure
4. Mean arterial pressure
5. Systolic pulmonary artery pressure
6. Diastolic pulmonary artery pressure
7. Mean pulmonary artery pressure
8. Pulmonary capillary wedge pressure
9. Central venous pressure
10. Cardiac output

The following derived hemodynamic variables were also analyzed:

1. Rate pressure product
2. Triple index
3. Cardiac index
4. Stroke volume
5. Stroke index
6. Left ventricular stroke work index
7. Systemic vascular resistance
8. Pulmonary vascular resistance

Figure 1 outlines the overall protocol schema.

FIGURE 1

PROTOCOL SCHEMA

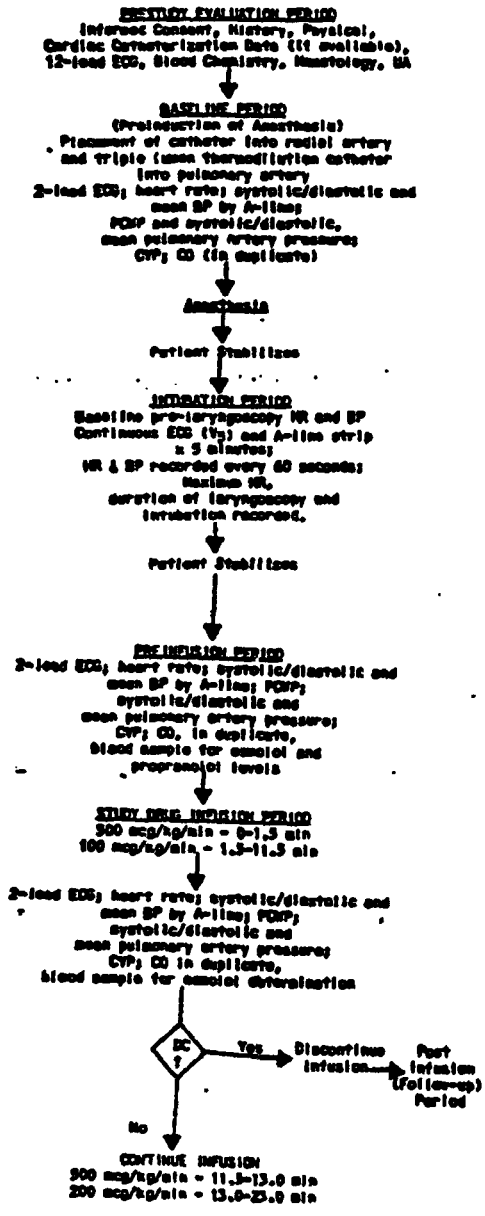
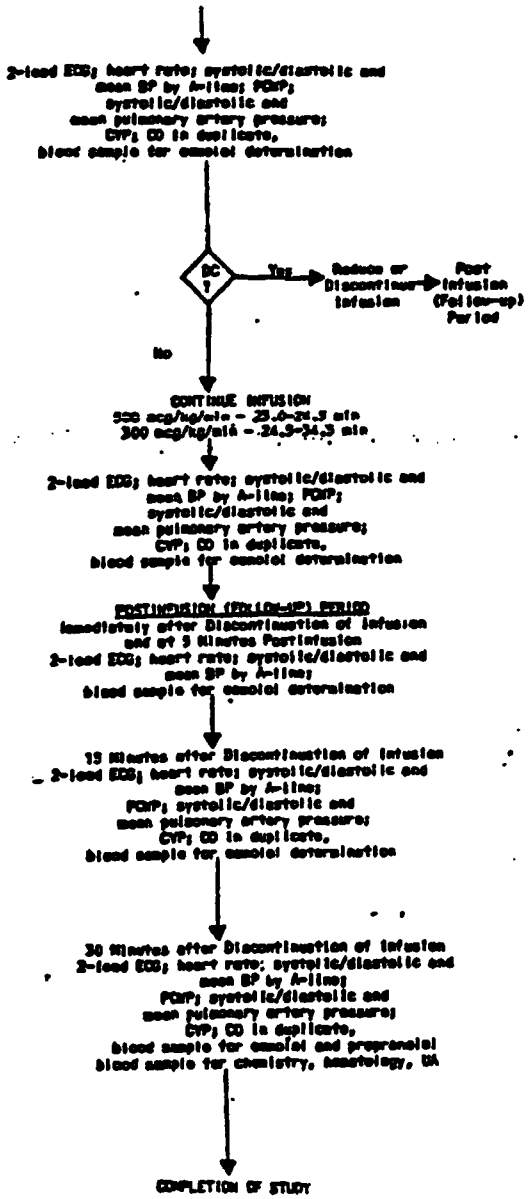


FIGURE 1 (continued)



Study Results

1) Except for one parameter, no statistically significant differences were detected between the esmolol and placebo groups for any of the hemodynamic parameters measured. Only the LVSWI showed a significant difference between the esmolol and placebo groups at the end of the 300 mcg/kg/min dose of esmolol (Table 7).

TABLE 7

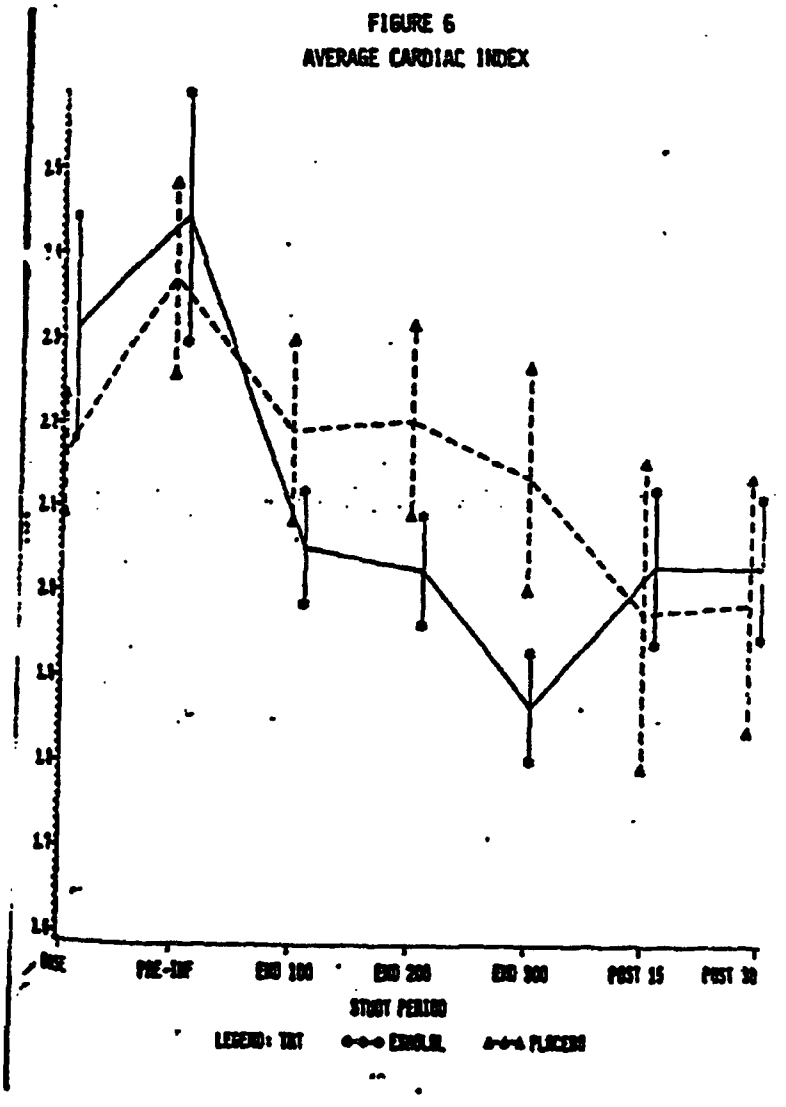
CARDIAC INDEX, STROKE VOLUME, STROKE INDEX, AND LEFT VENTRICULAR STROKE WORK INDEX, BY GROUP AND PERIOD (ELIGIBLE PATIENTS)

		PERIOD													
		BASELINE		* PREINFUSION		END 100 MCG/KG/MIN		END 200 MCG/KG/MIN		END 300 MCG/KG/MIN		POST 15 MIN		POST 30 MIN	
		+E	P	E	P	E	P	E	P	E	P	E	P	E	P
CI (L/min/m²)	MEAN	2.3	2.2	2.4	2.4	2.1	2.2	2.0	2.2	1.9*	2.1	2.0*	2.0	2.0*	2.0
	SEM	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.2	0.1	0.1
	N	10	8	9	8	10	8	10	7	9	6	10	8	10	8
SV (mL/beat)	MEAN	67.1	67.4	66.3	65.6	63.2	62.0	65.0	65.6	61.4*	64.5	66.4	62.7	70.6	66.1
	SEM	3.3	6.0	3.4	3.7	2.7	3.2	2.8	5.3	2.7	4.9	3.1	4.7	3.1	5.1
	N	10	8	9	8	10	8	10	7	9	6	10	8	10	8
SI (mL/beat/m²)	MEAN	36.3	36.2	36.4	34.6	34.0	33.9	35.0	35.3	33.0*	34.2	36.7	33.9	38.0	35.0
	SEM	2.0	2.6	2.1	2.2	1.4	1.8	1.5	2.6	1.5	2.2	1.1	2.2	1.4	1.3
	MIN	29	30	29	29	26	23	28	23	26	27	31	22	29	31
	MAX	47	48	45	45	39	39	41	45	40	41	42	42	44	48
	N	10	8	9	8	10	8	10	7	9	6	10	8	10	8
LVSWI** (gM/m²)	MEAN	43.0	39.9	40.2	36.8	37.3	34.3	37.1	39.2	34.4*	37.8	39.2	39.7	39.7	36.9
	SEM	4.1	2.4	3.4	2.8	1.7	2.3	2.1	3.6	2.4	4.9	2.8	3.9	2.6	2.2
	N	10	8	9	8	10	8	10	7	9	6	10	8	10	8

\+ E = esmolol P = placebo
* Significant change from baseline ($p < 0.05$)
** The change from baseline for LVSWI was greater in the esmolol group than the placebo group at the end of the 300 mcg/kg/min infusion.

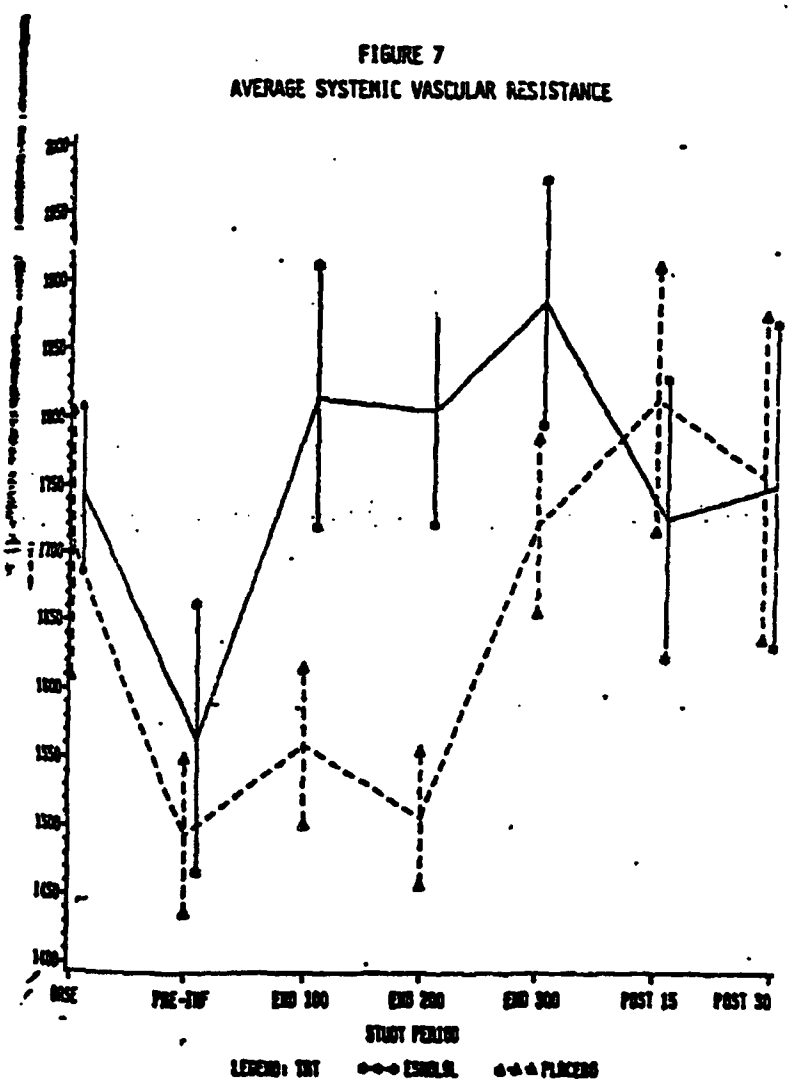
However, differences between the groups for a number of hemodynamic variables approached statistical significance. As can be seen in Figure 6 for example, the net reduction in cardiac index in the esmolol group is greater than that for the placebo (though not statistically significant at the end of the 200 and 300 mcg/kg/min infusion periods).

FIGURE 6
AVERAGE CARDIAC INDEX



Additionally, Figure 7 shows that the increase in systemic vascular resistance was greater in the esmolol than the placebo group.

FIGURE 7
AVERAGE SYSTEMIC VASCULAR RESISTANCE



There were significant changes from baseline (within group changes) for several variables in the esmolol group such as SBP, RPP, CVP, CO, CI, SV, SI and LVSWI. Significant decreases from baseline were found in each of these variables at the end of each dosage level of esmolol. Hence this linear pattern of activity is consistent with a probable esmolol dose effect response for these variables. As can be seen from Table 4 there was a greater reduction in systolic blood pressure for the esmolol group at 5, 15 and 30 minutes post infusion.

Table 4

HEART RATE, SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE, AND MEAN ARTERIAL PRESSURE, BY GROUP AND PERIOD (ELIGIBLE PATIENTS)

		PERIOD																	
		BASELINE		PRE INFUSION		END 100 MCG/KG/MIN		END 200 MCG/KG/MIN		END 300 MCG/KG/MIN		EOI* INFUSION		POST 5 MIN		POST 15 MIN		POST 30 MIN	
		E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P	E	P
HR	MEAN	69.3	61.1	67.3	70.1	61.0	66.5	59.6	65.6	57.6	63.2	58.0	68.0	59.1	69.4	59.1**	70.5	59.5**	70.4
(bpm)	SEM	3.2	4.5	4.1	4.6	3.9	4.9	3.9	4.8	3.9	4.9	3.5	5.0	3.8	5.5	3.8	5.4	3.9	5.1
	N	10	8	9	8	10	8	10	7	9	8	9	8	10	8	10	8	10	8
SBP	MEAN	140.3	137.9	137.8*	139.4	128.6*	135.6	127.1*	134.3	129.2*	137.0	128.1*	138.1	128.3*	137.4	128.8*	135.3	130.4*	135.0
(mmHg)	SEM	6.2	6.7	5.8	6.8	5.1	6.8	4.5	5.5	4.8	11.5	4.8	9.0	6.6	8.2	5.7	9.5	6.2	5.8
	N	10	8	9	8	10	8	10	7	9	8	9	8	10	8	10	8	10	8
DBP	MEAN	78.1	83.2	85.4	84.0	80.1	83.6	87.3	84.6	87.4	87.5	86.1	84.1	92.6	89.3	88.7	84.8	84.6	83.7
(mmHg)	SEM	4.1	1.6	3.0	3.0	3.6	3.8	2.9	2.5	4.1	4.8	3.3	4.3	3.3	4.7	3.8	3.3	2.8	2.7
	N	10	8	9	8	10	8	10	7	9	8	9	8	10	8	10	8	10	8
MAP	MEAN	98.1	99.9	99.9*	98.8	91.9	95.9	97.2	94.8	99.7	98.8	99.8	98.8	94.3	89.5	88.8	98.8	88.9**	88.5
(mmHg)	SEM	4.3	3.2	3.3	3.9	4.8	3.8	4.2	4.4	4.2	5.4	4.3	5.1	4.5	5.2	4.4	4.2	3.8	2.8
	N	10	8	9	8	10	8	10	7	9	8	9	8	10	8	10	8	10	8

* E = esmolol P = placebo
* Significant change from baseline ($p < 0.05$)
** The change from baseline for SBP was greater in the esmolol group than the placebo group at post-infusion five, 15 and 30 minutes.

2) In addition to the above data, the sponsor has also plotted several key variables (HR, SBP, RPP, SVR and CI) in a more detailed format for the esmolol and placebo groups. See Appendix 1B. In general, each of these variables ordered in terms of response to increasing doses of esmolol. This suggests that in the presence of anesthesia, the dose response curve for these variables may be altered. The potential implications for their effect are discussed in the analysis and comment section.

3) Measurement of blood levels of esmolol and its metabolite revealed findings consistent with the previous studies. For example the steady state blood levels of esmolol increased linearly over the dose or dosage range 100-200-300 mg/kg/min. After stopping the infusion, esmolol levels rapidly diminished and 30 minutes after termination of the infusion, either no esmolol was detected or the levels were only at the minimum quanifiable levels. As expected the blood levels of the esmolol metabolite continued to increase through the 30 minutes post infusion time.

As has been noted in other studies, (see study #14), the steady state blood levels of esmolol found in the arterial samples were significantly higher than those found in venous samples. The increasing amounts of metabolite in the blood over the entire study period is consistent with a longer half life of the metabolite.

Blood Levels of Esmolol and Its Metabolite

			End of			Post	Post	Post
		Preinfusion	100	200	300 mcg/kg/min	5 min	15 min	30 min
Esmolol (mcg/mL)	Mean S.D. N	Not detected (or <BQL*)	1.25 ±0.25 9	2.68 ±0.56 9	4.19 ±1.13 9	0.35 ±0.16 9	0.12 ±0.04 7	0.07 ±0.01 4
ASL-8123 Metabolite (mcg/mL)	Mean S.D. N	Not detected (or <BQL*)	1.83 ±0.11 4	3.56 ±1.33 9	8.85 ±1.36 8	9.32 ±1.57 9	10.00 ± 1.53 9	10.80 ± 1.58 8

Adverse Effects

Only one adverse effect was reported by the investigator in this study and this occurred in patient (19) who received placebo. This patient exhibited bradycardia (47 bpm) and low cardiac index (1.5 l/min/meter^2) at the end of the first titration period. The placebo infusion was discontinued because of this adverse hemodynamic findings. Evaluation of EKG abnormalities revealed no changes consistent with myocardial ischemia. Although only one patient was reported to have an adverse effect, 3 additional patients (one in the esmolol group) were prematurely terminated from the study. Patient #12 (esmolol group) had a low CI and increasing PCW at the end of the 200 mcg/kg/min dose of esmolol. Although only one patient was officially terminated, review of the data reveals that there were 8 patients who exhibited 1 or more of the hemodynamic safety checkpoints (criteria for termination of the infusion) yet the study medication was not stopped. The investigators did not believe that the patient's safety would be jeopardized even though they exhibited the hemodynamic checkpoints predefined and hence the infusions were continued. Seven of these 8 patients were in the esmolol group. This means that 8 of the 10 esmolol treated patients exhibited one or more of the hemodynamic checkpoints (see data below).

Hemodynamic Endpoint	Patient Number	
	Esmolol Group	Placebo Group
CI <2.0 L/min/m^2	4,5,8,13,20	3
HR <50 bpm	4	-
PCWP >20 mm Hg	2	-

Analysis and Comment

This study provides important data re: esmolol mediated hemodynamic effects in CABG patients that bear on study 49. The drug dosage and duration in study 25 was very similar to the treatment schedule followed in study 49. However in study 25 esmolol was given after intubation whereas in study 49 esmolol was started prior to intubation. Hence, study 25 is more of an esmolol tolerance study during anesthesia since a major adrenergic stress (intubation) has been avoided. Although only one variable (LVSWI) showed statistically significant differences between esmolol and placebo, there were clear cut trends for several other hemodynamic parameters including cardiac index (Figure 6), SBP and systemic vascular resistance (Figure 7). Moreover the majority of hemodynamic variables demonstrated a linear pattern (ordered) at each dosage step consistent with a esmolol dose effect for these variables. In addition although only one patient in the esmolol group was terminated prematurely, 7 other esmolol treated patients exhibited one or more of the hemodynamic/safety checkpoints and theoretically could have been terminated. Hence 8 of the 10 patients in the esmolol group exhibited significant hemodynamic checkpoints. This study in CABG patients along with the results in the carotid artery patients in study #49 (4 cases of myocardial ischemia) are quite suggestive that esmolol at the dosages employed might pose potential and serious cardiovascular ADE for CABG patients and/or patients with carotid artery disease. One question that arises from this analysis is why the majority of the patients in study 25 exhibited hemodynamic safety checkpoints. One possible explanation relates to the potential enhancement by anesthesia. It would be expected that a beta blocker would result in a decrease in left ventricular inotropic function (decreased cardiac index) with a resultant compensatory increase in systemic vascular resistance. This latter could also be blunted by anesthesia. In this regard, a comparison of study 14 which also includes patients with CAD but without anesthesia with study 25 should be instructive (see table).

Table
Comparison of Esmolol Mediated Hemodynamic Effects in Patients with CAD

	Study #14 (12 patients)		Study #25 (10 patients)	
	Baseline	Mean Reduction	Baseline	Mean Reduction
HR	73	4	64.3	6.7
SBP	152	15	149.7	28.5
CI	2.88	0.50	2.30	0.4
SVI	40	5.0	36.30	3.3
SWI	50	10	43	8.6
LVEF	74	14	-	-

Interestingly, the net mean reductions in several hemodynamic parameters (CI, SVI, SWI) are very similar in both studies. However, the net mean reduction in SBP is clearly greater in study 25. This is possibly related to potentiation of esmolol's effect on systolic blood pressure by anesthesia. Several explanations could be invoked to explain the changes in hemodynamic variables associated with esmolol infusion. These include the fact that the compensatory increase in systemic vascular resistance which would accompany the esmolol induced decrease in cardiac output may not be as effective as it

would be in normal or unanesthetized patients in restoring adequate systemic vascular resistance. Another possibility as suggested by the dose response effect of esmolol is that the level of the maintenance dosage employed in these studies (300 mcg/kg/min) is too high in these patients. These results suggest that it may be necessary to adjust the dosage of esmolol in the maintenance phase in order to avoid depressing these hemodynamic variables during anesthesia.

Addendum to Study 25

A comprehensive (comparative) summary of the major hemodynamic responses monitored in CAD patients in the esmolol studies has been submitted by the sponsor in response to our request (see tables below). Analysis of this data is complicated by the fact that the baseline hemodynamic data listed for patients in studies 14 and 25 in the new tables differs significantly from the figures reported in the NDA. The discrepancy in study 14 probably reflects the fact that only 6 patients with CAD were analyzed as opposed to 12 patients (entire study group) in the NDA. However, there is no obvious explanation to account for the gross differences in the baseline values in Study 25 [SBP-130 vs SBP-149.7 (NDA)]. This latter discrepancy completely changes both the result (the net reduction in SBP goes from 28.5 to 8.4 mm Hg) and the interpretation since this parameter was the one most significantly altered by esmolol.

HEMODYNAMIC DATA (MEAN) BY STUDY IN PATIENTS WITH CORONARY ARTERY DISEASE

	INVESTIGATOR (STUDY NUMBER)					
	ASHIMAKI (8082-82-14)		KAPLAN (8082-82-25)			
			ESMOLOL		PLACEBO	
VARIABLE[a]	BASELINE (N=6)[b]	ESMOLOL (change from baseline)	BASELINE (N=3)[b]	INFUSION (change from baseline)	BASELINE (N=6)[b]	INFUSION (change from baseline)
HR (bpm)	71	-3.2	67	-0.7	74	-11.2
SBP (mm Hg)	140	-12.9	130	-8.4	134	4.8
DBP (mm Hg)	81	-2.2	84	2.2	87	0.3
PCWP (mm Hg)	10.8	2.7	7.0[c]	8.0[cc]	11.7[c]	0.0[cc]
CI (L/min/m^2)	2.7	-0.5	2.4	-0.01	2.4	-0.27
SVI (mL/m^2)	37.7	-4.8	36.8	-2.8	32.4	1.3
LVSWI (g m/m^2)	48.8	-9.8	38.4	-6.1	34.6	2.1
SVR (d s cm^{-5})	1543	314	1540	333	1911	253
DOSE (mcg/kg/min)	---	300	---	300	---	---

[a] Six eligible patients also had documented CAD.
[b] Of the 18 eligible patients, nine patients who received esmolol and six who received placebo had complete infusion period data. All these patients were anesthetized with fentanyl.
[c] Significant difference in baseline values between esmolol and placebo (p<0.05).
[cc] Significant difference in change from baseline between esmolol and placebo (p<0.05).

HEMODYNAMIC DATA (MEAN) BY STUDY IN PATIENTS WITH CORONARY ARTERY DISEASE

	INVESTIGATOR (STUDY NUMBER)					
	KLONER (8052-82-33)		SHAMPAIN (8052-82-13)[a]			
			ESMOLOL (REST)		PROPRANOLOL (REST)	
VARIABLE	BASELINE (N=10)[b]	ESMOLOL (change from baseline)	BASELINE (N=7)[b]	INFUSION (change from baseline)	BASELINE (N=6)[b]	INFUSION (change from baseline)
HR (bpm)	92	-17.1[c]	74	-10.1[c]	84	-0.2
SBP (mm Hg)	117	-17.2[c]	142	-11.4[c]	142	-13.2
DBP (mm Hg)	85	-0.2	98	-7.7	84	-0.4
PCWP (mm Hg)	13.8	1.4	---	---	---	---
CI (L/min/m^2)	2.8	-0.64[c]	2.9	-0.5[c]	2.6	-0.3
SVI (mL/m^2)	32.5	-2.4	---	---	---	---
LVSWI (g m/m^2)	32.6	-0.8	---	---	---	---
SVR (d s cm^{-5})	1910	147	---	---	---	---
DOSE (range)	---	793 mcg/kg/min (139 - 300)	---	300 mcg/kg/min	---	6 mg

[a] Ten of the 10 total patients had complete maintenance period.
[b] Of the 17 patients with documented CAD, seven were initially randomized to receive esmolol and five were randomized to receive propranolol.
[c] Change is significantly different from zero (p=0.05).
[d] Changes from baseline did not differ significantly between esmolol and propranolol (p=0.05).

iii. Cardiac Electrophysiology (EP)

Study 8052-82-13

Objective

To assess the cardiac EP effects of esmolol administered by IV infusion to patients hospitalized for routine diagnostic EP testing.

Study Design and Patients

The study was conducted in an open label manner. Seventeen patients (11 males and 6 females) were selected by the investigator from a population hospitalized for routine diagnostic electrocardiographic testing. The patients ranged in age from 24-75 years. Six of the 17 patients had a history of coronary artery disease. Data from 14/17 patients were eligible for the EP analysis. Data from all 17 patients were analyzed for safety.

Treatment Plan and Test Parameters for Safety and/or Efficacy

A loading dose of 500 mcg/kg/min for 3-5 minutes followed by maintenance infusion of esmolol 300 mcg/kg/min for a total infusion time of 13-45 minutes. Efficacy was evaluated by the determinations of SA nodal function, atrial conduction time, atrial refractoriness, AV node and his-purkinje system function, ventricular function and retrograde conduction; 12 lead ECG.

Study Results

The following EP effects of esmolol were noted:

1. Decrease in heart rate (7.8 ± 1.9 bpm).

2. Prolongation of sinus node recovery time (88.6 ± 28.5 msec).

3. Prolongation of AH interval during normal sinus rhythm (5.8 ± 2.3 msec) and during atrial pacing (cycle length 600 msec) (10.8 ± 3.7 msec).

4. Increase in antegrade Wenckebach cycle length (37.1 ± 13.4 msec).

5. In addition, to the above, no significant changes in surface ECG intervals (PR, QRS and QT), sinus node recovery time, SA conduction time, HV interval were noted.

6. No significant differences were detected in the various EP parameters between CAD and non-CAD patients.

Thirty minutes following termination of the esmolol infusion several significant changes (from baseline) were observed.

1. Increase in heart rate (6.3 ± 2.8 bpm).

2. Shortening of sinus and corrected sinus node recovery time (146 ± 41 and 53 ± 20 msec, respectively).

3. Shortening of paced AH interval (24 ± 9 msec).

4. Shortening of the AV nodal effective refractory period at 450 msec pacing cycle length (40 ± 11 msec).

5. Shortening of the AV nodal functional refractory period at 600 msec pacing cycle length (31 ± 13 msec).

6. Shortening of the atrial effective refractory period during 600 msec pacing (21 ± 9 msec).

Safety Results

Five of the 17 patients exhibited 1 or more of the following adverse effects: hypotension (n=2), diaphoresis (n=2), atrial flutter (n=1), chest tightness/pressure (n=2), bradycardia (n=1), vasovagal reaction (n=1) and vomiting (n=1). During the infusion of esmolol, the average heart rate and systolic blood pressure decreased significantly from control values of 80 ± 3 bpm and 126 ± 4 mm Hg to 69 ± 3 bpm and 106 ± 5 mm Hg respectively. However mean values for heart rate and blood pressure returned to approximately baseline levels within 30 minutes following completion of the esmolol infusion. In general the bradycardic and hypotensive effects occurred only during esmolol infusion and were transient in nature. The 12 lead ECGs obtained during the post study period were not appreciably different from those obtained during the prestudy period. Mean blood levels of esmolol during the steady state maintenance infusion in parallel with EP testing and observed EP effects were 0.842 mcg/ml in patients receiving 500 mcg/kg/min

loading dose for 3 minutes and 0.967 and 1.46 mcg/ml in patients receiving a loading dose for 5 minutes. At 30 minutes post infusion esmolol levels were either significantly reduced or below the detectable limit. In contrast levels of the acid metabolite of esmolol increased during the infusion and continued to increase at 30 minutes following the termination of esmolol infusion.

Conclusion

In conclusion, esmolol produced modest but statistically significant EP changes consisted with beta adrenergic blockade: heart rate and AV nodal conduction were depressed and AV nodal refactoriness as indicated by Wenckebach cycle length, was increased. During the post infusion period modest but significant changes compared to baseline in the opposite direction were observed. It is not clear whether the observed effects were related to esmolol (rebound phenomenon) or due to temporal instability of the patients.

d. Drug Interaction Studies

Overview

Three clinical trials were conducted to examine potential drug interactions with esmolol. Two studies focused on pharmacokinetic aspects with morphine (study 8052-83-38) and digoxin (study 8052-83-39). A third completed study examined the clinical interaction of esmolol and succinylcholine (study 8052-83-48). In addition, a fourth study in progress is designed to examine the pharmacokinetic interactions between esmolol and warfarin (Interim report volume 3.23). There have been no indications of any clinical interactions between the two drugs (from the adverse experience reports).

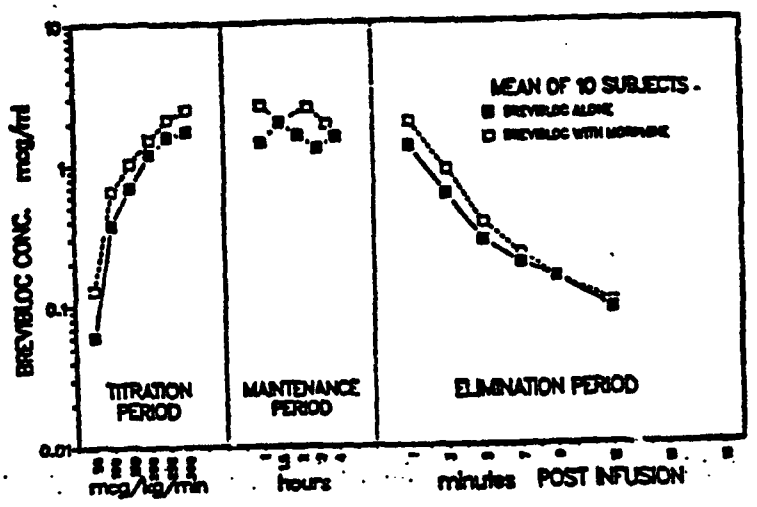
1. Study 8052-83-38

Study Design, Drug Dosage and Test Parameters for Safety and/or Efficacy

This was an open label determination of the interactions between esmolol and morphine involving 10 normal males. Esmolol was titrated from 50 mcg/kg/min to 300 mg/kg/min over 30 minutes followed by a 3.5 hour infusion of 300 mcg/kg/min. Morphine sulfate 3 mg was given by slow IV injection.

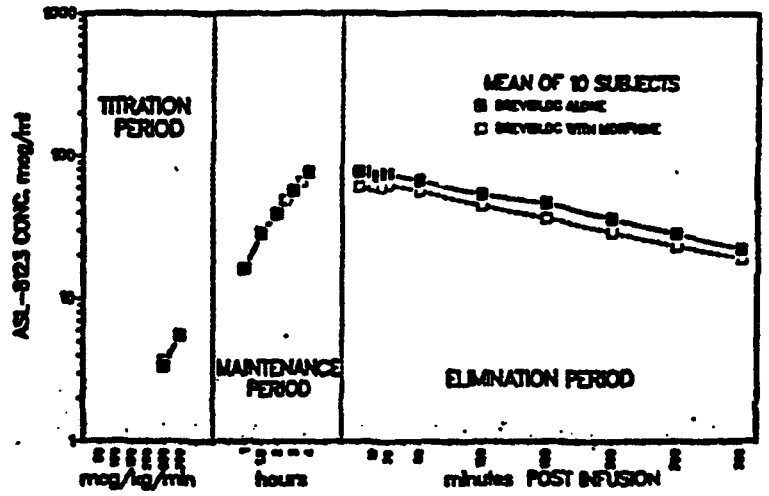
Study Results

As can be seen in the following figure, the mean steady state blood level of esmolol was significantly higher (46%, p less than 0.05) during the morphine/esmolol period.



However, Morphine had no effect on the half life of esmolol. In addition, morphine had no effect on the blood levels, total body clearance, elmination rate constant, and terminal elmination half life of the acid metabolite of esmolol.

In addition, morphine serum levels were very similar with and without esmolol treatment. Therefore esmolol did not appear to have any effect on the area under the concentration time curve (AUC) and terminal elimination half life of morphine. In conclusion, morphine may increase steady state blood levels of esmolol but esmolol does not cause any changes in the pharmacokinetics of morphine.



Study 8052-83-39

Study Design

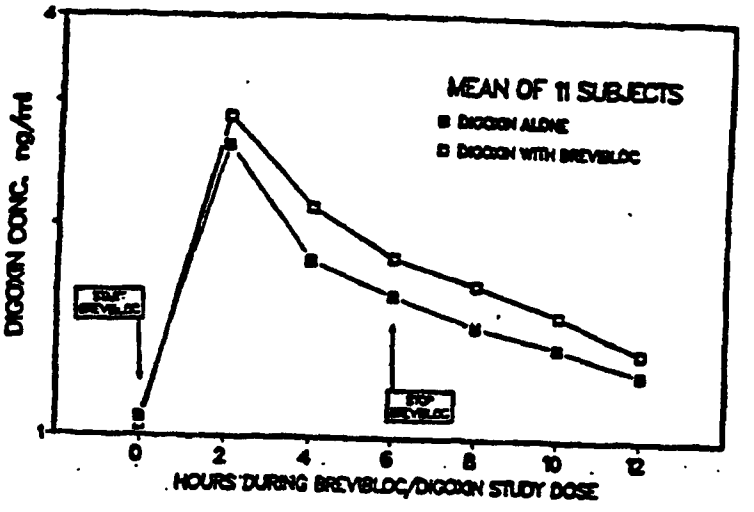
This was an open label study of the pharmacokinetics and pharmacodynamics between esmolol and digoxin. The study involved 12 normal male subjects.

Study drug dosage and test parameters for safety and/or efficacy

A 6 hour esmolol infusion titrated from 50-300 mcg/kg/min before and during digoxin therapy which was titrated to a serum digoxin level of 0.8 to 2.0 nanograms/milliliters.

Study Results

The steady state blood levels, the total body clearance, half lives and volume of distribution for esmolol did not show any significant changes between esmolol-digoxin treatments. In addition, there were no significant differences in half lives or maximum blood levels of the acid metabolite between esmolol and esmolol-digoxin treatments. As can be seen in the following figure esmolol did have an effect on digoxin levels.



Serum digoxin levels increased 9.6 to 19.2% during the esmolol-digoxin treatment compared to digoxin alone. The total area under the digoxin concentration vs time curve (AUC) during the 6 hour esmolol infusion was significantly higher in the presence of esmolol than when digoxin was given alone. No significant change in peak digoxin levels were observed. According to the sponsor only the four hour digoxin serum level was significantly elevated when the two treatments were compared by subject. According to the sponsor caution should be exercised in using the drugs in combination because digoxin levels may be slightly elevated during esmolol infusion.

Study 8052-83-48

Study Design

This was an open label nonrandomized placebo controlled parallel study of the effect of esmolol on heart rate and blood pressure increases related to endotracheal intubation and on the duration of succinylcholine-induced neuromuscular blockade in patients anesthetized with thiopental.

Patients

These patients were anesthetized noncardiac elective surgery patients. Eighteen patients age 22-57 years were entered into the study and received placebo (10) or esmolol (8) in an alternating fashion.

Drug dosage and test parameters for safety and/or efficac,

The study drug dosage was administered according to the following schedule: 500 mcg/kg/min for 4 minutes followed by 300 mcg/kg/min for 8 minutes. This is the same dosage regimen used in the perioperative studies (see the

perioperative studies for clinical efficacy). Efficacy parameters included heart rate and blood pressure determinations and continuous muscular twich measurements. Continuous recordings of muscle twitch response were made throughout the study period using the strength of thumb adduction as measured by a force-displacement transducer.

Study Results

A. Efficacy

Esmolol significantly blunted the increase in rate pressure product when compared to placebo that occurred in response to the stimulus of endotracheal intubation. This was of interest since the components of rate pressure product, namely heart rate and systolic blood pressure when analyzed separately did not show statistical significance. However, there was a tendency for esmolol to blunt the increase in both heart rate (47 bpm for the placebo group vs 30 bpm for the esmolol group) and systolic blood pressure (44 mm Hg for placebo, 20 mm Hg for esmolol) following endotracheal intubation. In addition, 8 patients in the placebo group had a heart rate greater than 100 bpm following intubation as compared to only 1 esmolol treated patients. This difference was statistically significant.

B. Neuromuscular Blockade

The esmolol group had a signficantly prolonged duration of succinylcholine-induced neuromuscular blockade compared to the placebo group. As can be seen in the figure below, the average difference in the time of recovery of twitch response between the two groups was almost 3 minutes. According to the sponsor this prolongation of neuromuscular blockade is not considered to be clinically important, as twitch recovery times for all esmolol patients were within the range of variability in response to succinylcholine at the dosage used in the study. In addition, the onset of maximal twitch depression was similar in both the esmolol and placebo groups. The mechanism of prolongation of muscle paralysis in the esmolol group is unclear.

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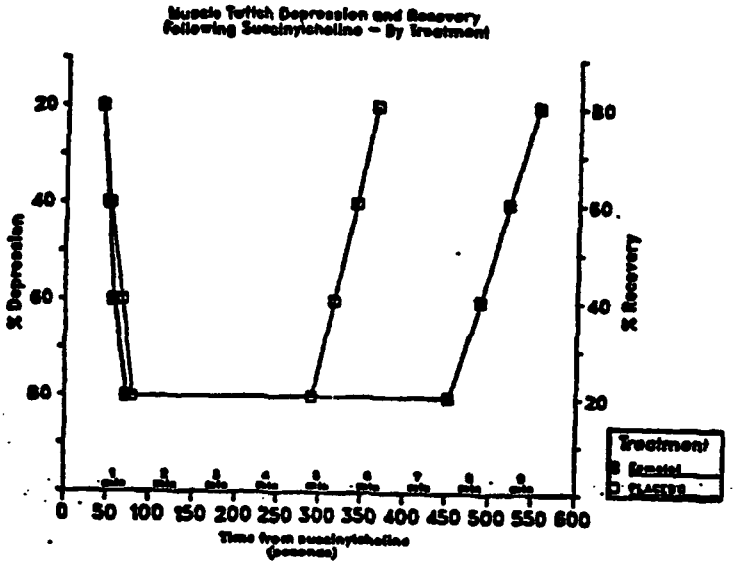

Safety Results

Safety was assessed in all 18 patients. No adverse effects were noted in any patients.

Analysis and Comment

In all three of these studies, esmolol, digoxin, morphine and succinylcholine were well tolerated when administered alone or in combination with each of the other agents. In view of the results of these interaction studies, esmolol should be administered with caution in patients receiving digoxin concurrently. When administered concurrently with morphine, the dosage of esmolol may be adjusted as required to achieve the desired effect. It is unclear as to the clinical significance of the interaction between succinylcholine and esmolol. If necessary, the dosage of esmolol may be reduced or discontinued.

e. Other Studies

Esmolol was also considered for possible application in the treatment of glaucoma. Therefore, two ocular tolerance studies were conducted in normal volunters studies 8052-82-11 and 8052-82-19. However, this program was subsequently discontinued in favor of an alternative compound and no other ocular studies were initiated with esmolol. For these reasons, results of these studies will not be discussed further.

2. Dose Ranging Studies

Overview Summary

Dose Response (Range) Studies

A. SVT

Results of a single dose range study (8052-81-07) constitute the evidence provided by the sponsor in support of demonstrating a dose response effect on ventricular rate in SVT. The data is consistent with esmolol producing a modest (20%) reduction in ventrical rate over the dose range assessed (50, 100, 150 and 200 mcg/kg/min). All parameters studied (HR, SBP, DBP and RPP) ordered in terms of change with increasing doses of esmolol. Perhaps the most convincing evidence for an effect is the finding that these parameters recover (HR and SBP) when the drug infusion is stopped. The actual magnitude of the response is obscured by the fact that all parameters decreased as much during the placebo baseline period as they did during the study period. Therefore, it is probably an over interpretation of the data to conclude that there was a dose dependent response. Another important finding is the fact that recovery from the effect (i.e., return of HR and SBP toward baseline) correlates with decreasing blood levels of esmolol while blood levels of the acid metabolite are increasing. This is consistent with esmolol being the active moiety while the acid metabolite is really inactive.

B. Perioperative Studies (Anesthesia)

The sponsors claim for evidence of an esmolol dose response relationship in attenuating intubation induced tachycardia and systolic hypertension are provided in three studies (8052-82-21, 8052-83-44 and 8052-83-45). In each study the primary response variables were HR, SBP and RPP.

i) Study 21 (CABG patients)

The results indicate that although each of the response variables orders in terms of change with increasing doses of esmolol, there were no statistically significant differences in the groups including control. Thus, there may be a dose response trend.

ii) Study 44 (non CABG patients)

Results of this study are negative. The response variables (HR, SBP and RPP) do not order or relate to increasing dose of esmolol. Clearly no dose response trend or effect is evident.

iii) Study 45 (non CABG patients)

These results indicate that one of the three response variables (HR) does show an ordered response to increasing doses of esmolol but again the differences between treatement groups are not statistically significant. The other two variables (SBP and RPP) clearly do not order or even remotely show a dose response trend or effect. It is interesting to note that the controlled clinical trials in the perioperative studies followed a dosing schedule very similar to that described for the Brevibloc 300 mcg/kg/min group.

While failure to demonstrate a clear dose response relationship in the three perioperative studies is not totally surprising, the lack of an ordered response in two of the trials (studies 44 and 45) except for the HR response in Study 45 is of concern. Further, it is somewhat surprising that the only trial (Study 21) which shows ordering of the response for all three variables differs the most in terms of its dosage schedule compared to the controlled clinical trials.

The following conclusions can be made re: the dose ranging pilot studies:

a) SVT - The data establishes that esmolol had an effect but doesn't clearly support that it was dose related (dependent).

b) Perioperative - The data doesn't consistently establish that esmolol had an effect let alone a dose-related effect.

a. Supraventricular Tachycardia (SVT)

Two specific dose range studies were initiated based on the blood level findings and simulations derived from one of the initial (pharmacokinetic) studies (8052-81-02). (See (b) Pharmacokinetic.) However one of the studies was not completed (8052-81-06) but the second (8052-81-07) was completed and is discussed in this section. The results of this study are very important because data derived from this study was used in the design of the controlled clinical studies and partially controlled trials.

Study 8052-82-07

Study Objectives

(1) To compare the efficacy of IV esmolol vs placebo on heart rate in patients with supraventricular tachyarrhythmias.

(2) To examine the safety of esmolol in these patients.

(3) To study blood levels of esmolol and its metabolite, ASL-8123.

Study Design

This was an early phase two single blind, baseline controlled pilot study involving patients with documented SVT.

Patients and Patient Selection

Twelve patients with stable SVT were entered in the study. The participants were selected from patients hospitalized with documented SVT (chronic atrial fibrillation, chronic atrial flutter, chronic atrial tachycardia or chronic sinus tachycardia with a ventricular rate of at least 90 beats per minute at rest.

Treatment Plan and Test Parameters for Safety and/or Efficacy

A 30 minute placebo baseline infusion was followed by a 29.5 minute infusion of esmolol at 50, 100, 150 and 200 mcg/kg/min. Each esmolol infusion was preceeded by a 0.5 minute loading dose of 500 mcg/kg/min. The four primary efficacy variables were heart rate, systolic blood pressure, diastolic blood pressure and double-product.

Statistical Methodology

The averages over the 3 measurement times (5, 10 and 30 minutes during the infusion) at each dosage were used as a data for analysis for each patient.

Study Results

Patient Characteristics

At the time of the prestudy examination, 6 of the 12 patients were diagnosed as having atrial fibrillation. One patient had sinus tachycardia and one patient was in atrial flutter. Apparently no specific interpretations were given for the last 4 patients.

Protocol Deviations

Three patients were included in the efficacy results (patient 3, 5 and 8) which according to the study criteria should have been dropped from the study. Patient 3 received verapamil within two half lives of the study but was included anyway. Patients 5 and 8 with baseline average heart rates of 88 and 87 beats per minute were also included even though the cut off was 90 beats per minute. In addition, patient 10 developed hypotension (blood pressure 75/50 mm Hg and did not complete the study). The patient was excluded from efficacy analysis.

Efficacy Results

A summary of the overall findings are illustrated the following figures and tables (Figure 1, Figure 2, Figure 4, Figure 5 and Table 2).

Table 2: Summary of Heart Rate, Systolic and Diastolic Blood Pressures, and Double Product

(Average ± Standard Error)

Dosage	Heart Rate (bpm)	Heart Rate Decrease β	SBP (mm Hg)	Δ SBP	DBP (mm Hg)	Δ DBP	Double[1] Product	Double Product Decrease (1)
Prestudy	119.82 ± 4.60	---	138.18 ± 7.61	---	88.64 ± 3.64	---	16.57 ± 1.08	---
(Placebo) Baseline	111.86 ± 6.31	---	140.00 ± 6.97	---	90.38 ± 3.62	---	15.54 ± 1.01	---
Esmolol 50 mcg/kg/min	101.95 ± 5.60	8.05 ± 1.41**	134.70 ± 7.50	-5.30 ± 1.36**	85.61 ± 3.60	-4.70 ± 0.80**	13.66 ± 0.84	11.76 ± 1.45**
Esmolol 100 mcg/kg/min	90.85 ± 5.47	11.39 ± 1.36**	127.88 ± 8.08	-12.12 ± 1.83**	82.12 ± 3.54	-8.10 ± 0.69**	12.49 ± 0.86	19.64 ± 1.41**
Esmolol 150 mcg/kg/min	95.91 ± 4.83	13.87 ± 1.68**	124.39 ± 8.26	-15.61 ± 3.24**	82.12 ± 4.11	-8.80 ± 1.41**	11.82 ± 0.86	23.78 ± 2.41**
Esmolol 200 mcg/kg/min	94.70 ± 4.99	14.74 ± 1.78**	120.91 ± 7.76	-19.09 ± 2.73**	79.70 ± 3.37	-10.61 ± 1.66**	11.31 ± 0.74	26.72 ± 2.91**
(Placebo) Post Infusion								
5 min	102.00 ± 4.56	7.09 ± 2.31*	129.00 ± 7.66	-13.00 ± 2.70**	82.27 ± 3.49	-8.03 ± 1.36**	12.61 ± 0.76	18.10 ± 2.66**
15 min	104.00 ± 5.12	6.48 ± 1.56**	127.27 ± 7.99	-12.73 ± 2.09**	84.00 ± 3.08	-6.21 ± 1.76*	13.10 ± 0.89	13.36 ± 2.33**
30 min	106.73 ± 5.83	3.73 ± 2.17	129.55 ± 8.43	-10.45 ± 3.66*	87.27 ± 3.55	-3.83 ± 1.88	13.75 ± 1.02	11.53 ± 2.71**
Poststudy[2]	113.36 ± 4.93	5.41 ± 1.78*	136.36 ± 7.17	-1.82 ± 2.05	88.18 ± 3.46	0.45 ± 0.76	15.39 ± 0.90	0.45 ± 2.58*

* (**) Indicates significant change from placebo control baseline ($p \leq .05$ (.01)

(1) Double product = $\frac{\text{(heart rate)} \times \text{(systolic pressure)}}{1000}$

(2) Poststudy changes are from the prestudy levels

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

Δ = Change

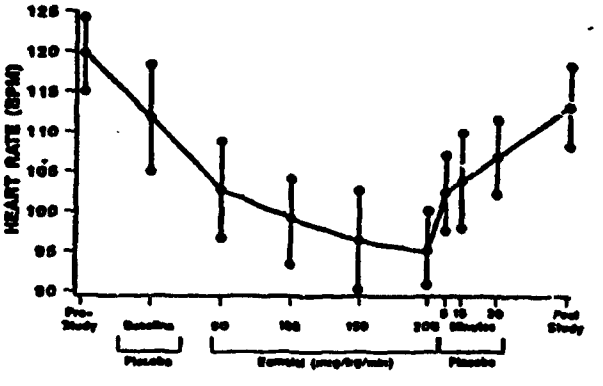

Fig. 1 Effect of esmolol on heart rate (average ± s.e.m.)

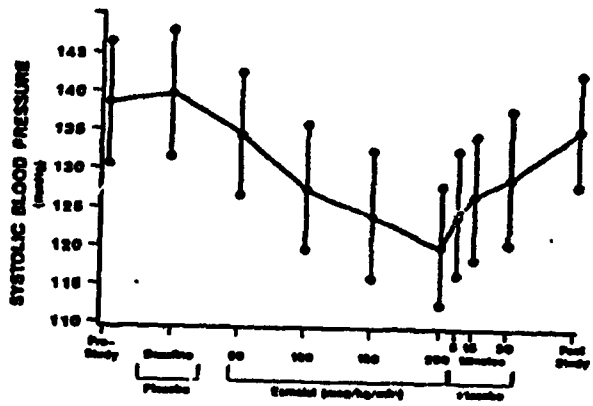

Fig. 2 Effect of esmolol on systolic blood pressure (average ± s.e.m.)

In summary. 11 of the 12 patients were considered for efficacy analysis. The ventricular heart rate, systolic and diastolic pressure and double product showed a decrease following esmolol when compared to placebo. Furthermore the reductions were generally greater with increasing doses of esmolol. There were no conversions to normal sinus rhythm. As can be seen from the accompanying figure (Figure 4), there was a dose dependent increase in esmolol blood levels over the period of infusion consistent with the PK data previously shown.

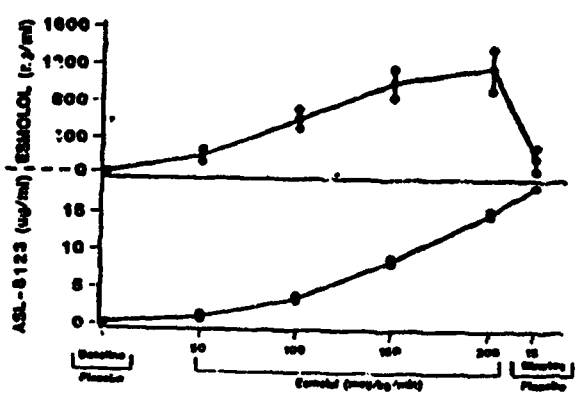

Fig. 4 Blood levels of esmolol and ASI-8123 (average ± s.e.m.)

N19-386 2 of 3 BIO PORTION OF MOR

For most patients esmolol blood levels seemed to correlate with the reduction in heart rate. As can be seen from the data, esmolol produced significant reductions in heart rate, systolic and diastolic pressure at all four dosages of esmolol. The positive relationship between heart rate and esmolol concentration in the blood is shown in Figure 5.

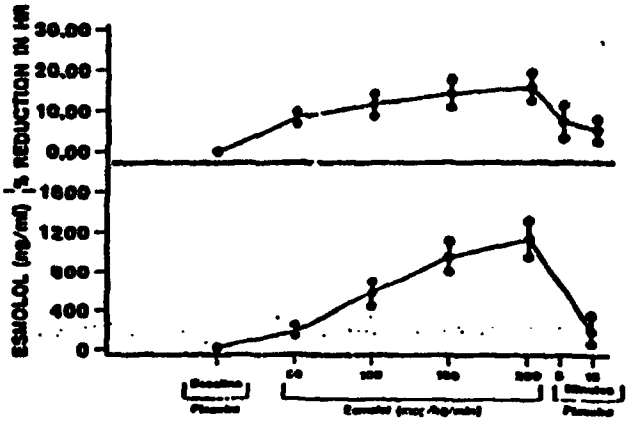

Fig. 5 Heart rate reduction and esmolol blood levels (average ± s.e.m.)

Hence, the data qualitatively supports the idea that esmolol had an effect but doesn't clearly support a dose response effect.

Safety Results

Adverse Effects

Four of the 12 patients exhibited ADE. The most serious ADE was observed in patient 10 who developed hypotension with dizziness and fatigue while receiving the 150 mcg/kg/min infusion of esmolol. This patient did not complete the study. The other 3 patients were able to complete the study.

Analysis and Comment

Three of the 12 patients included in the efficay analysis of this study should have been excluded based on the principal investigator's own exclusion criteria. It is not clear what effect excluding these three patients would have on the overall interpretation of the study. Recovery from beta blockade which is shown during the post infusion period reveals that significant differences still existed at 15 minutes (heart rate and diastolic blood pressure) and 30 minutes (systolic blood pressure and double product). Thus, the effects of esmolol persisted beyond the observed elimination half life of 9 minutes. That there was a significant recovery is probably the most convincing evidence that esmolol had an effect at all. This is due to the

fact that both SBP and HR drifted downward during the baseline lead in period and thus the observed effects would be due to time. In addition, although these results were used to design the clinical efficacy trials in SVT, it is important to note that several differences exist between this study and these subsequent trials. This includes the following: the patient selection criteria (chronic stable SVT), heart rate (90 vs 120), response criteria (X% vs 20%) as well as the duration of the maintenance infusion (30 minutes vs 4 minutes).

2. Dose Ranging Studies

b. Perioperative Studies (anesthesia)

Three open pilot studies study 8052-82-21, 8052-83-44, and 8052-83-45 were performed to assess the dose response relationship of esmolol in attenuating the tachycardia and hypertension associated with the stimulus of endotracheal intubation in anesthetized patients. The results of these 3 studies were used to formulate and design the controlled clinical studies that evaluated the safety and efficacy of esmolol for this indication.

The basic design, the study objectives, treatment plan, duration and method of efficacy assessment was similar in all three of these nonrandomized studies. The major differences revolved around the agent used for induction and the general anesthestic. In study # 1, patients received diazepam IV for induction whereas in study #2 they received thiopental for induction and in study #3 they received ketamine.

Study 8052-82-21

Objectives

To evaluate the safety and efficacy of different doses of esmolol in attenuating tachycardia and hypertension during endotracheal intubation of anesthetized CABG patients.

Study Design and Number of Patients

The design of the study was nonrandomized, open label with 4 groups, control (no treatment), esmolol: 100 mcg/kg/min, 200 mcg/kg/min and 300 mcg/kg/min. Forty-two CABG patients entered the study: placebo group n=10; esmolol 100 n=11; esmolol 200 n=10; and esmolol 300 n=11. Of these 42 "all patients" 38 were classifed as "efficacy patients". Analysis of the effect of esmolol on heart rate and other efficacy variables was thus restricted to the 38 efficacy patients. Safety analysis was based on the data for all 42 patients.

Treatment Plan and Test Parameters for Safety and/or Efficacy

All patients received diazepam I.V. for induction and pancuronium for muscle relaxation. The study consisted of 5 periods:

1. A pre-induction baseline period,
2. A 3 minute post induction (preinfusion) period,
3. A 3 minute preintubation period (esmolol infusion period),
4. A 4 minute post intubation period (esmolol infusion period),
5. And a 30 minute post infusion period.