CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-386

Clinical Pharmacology and Biopharmaceutics Review

Esmolol HCl (Brevibloc)
I.V. Injection
NDA-19-386
Reviewer: Donald L. Heald

American Critical Care
McGraw Park, Il 60085
Submission Date:
January 7, 1985

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Review of 3 Biostudies

Background:

Brevibloc (esmolol HCl) has a very short duration of pharmacological action in vivo because of its rapid metabolic inactivation. In animal studies it has been shown that this rapid inactivation occurs by hydrolysis of the methyl ester functionality in Brevibloc to the corresponding carboxylic acid (ASL-8123) via esterases in the cytosol of the RBC's and not by plasma cholinesterases or RBC membrane acetylcholinesterase. The drug must be administered by the intravenous route and continuous infusion is required to achieve a prolonged pharmacological response. The following studies defined the pharmacokinetics of Brevibloc and ASL-8123, approximately 1/1500 as potent as esmolol HCl, in humans and provide the basis for the dosage regimen developed.

It should be noted that since blood sampling does not stop the hydrolysis of the drug, rapid inhibition and denaturation of the esterase followed by separation of drug and metabolite was required. This was achieved by partial inhibition of the esterase via collection of samples in sodium fluoride and rapid denaturation and separation of drug and metabolites be addition of blood into methylene chloride. These steps had to be performed by the staff at the site of the clinical investigation by procedures transferred to the clinical site by the sponsor and validated prior to initiation of the clinical phase of the study.

Study 1:

Title: Dose proportionality pharmacokinetic study and effect of long term infusion on distribution and elimination of esmolol in normal subjects.

Objectives: To elucidate the pharmacokinetics of Brevibloc and its major metabolite (ASL-8123) over the dose range of 50-300 mcg/kg/min in normal subjects.

To examine the dose proportionality of the pharmacokinetics of the drug and metabolite.

To study the effect of long term infusion on elimination of Brevibloc and its metabolite, ASL-8123, in normal subjects.

ACC Protocol: 8052-82-09

Investigators:

John J. Hanigan, M.D.
Dwight L. Snyder, M.D.
Noble Swanson, M.D.
James E. McClurg, Ph.D.

Institution:
Harris Laboratories, Inc.; Lincoln, NE 68501

Study Design:
This was a restricted-randomized, crossover study. The subjects, clinical staff, and analytical staff were blinded, while the investigator was not. Each subject received 50, 100, 200, and 300 mcg Brevibloc per kg per min for 6 hours. Subjects were not permitted to receive the 200 mg dose before the 100 nor the 300 mg dose before the 200 mg dose. Thus, it was not a truly randomized study. All four of these treatments were separated by a one week interval. All subjects received a 150 mcg Brevibloc/kg/min dose for 24 hours in the fifth phase of the study. The fifth phase started two weeks after the start of the fourth phase.

Subject Selection:
Eight healthy, adult male subjects were selected by the investigator from the locally available population. The subjects ranged in age from 19 to 26 years. A complete history, physical examination, and laboratory evaluation prior to starting the study showed no evidence of any organic or functional disease. Normal inclusion and exclusion criteria. The subjects were randomized into four groups to determine the sequence of dosages of Brevibloc which they were to receive. All subjects signed a written informed consent.

Administration:
Brevibloc Injection: was supplied to the investigators as a sterile non-pyrogenic, clear, colorless solution in 10 ml clear glass ampuls containing 100 mg/ml of esmolol HCl.

Each 10 ml ampul (Lot #736-34) contained:

Esmolol HCl	1 g

All dosages, calculation, and measurements in this study are based on the hydrochloride form of the drug and hydrochloride form of the metabolite.

The diluent for all Brevibloc infusion was Dextrose (5%) Injection, USP. A final concentration of 10 mg/ml of Brevibloc was prepared by making a 1:10 dilution of Brevibloc in Dextrose (5%) Injection USP (D5W). This was done, for example, by removing 50 ml of D5W from a 500 ml container and replacing it with 50 ml (5 ampules) of Brevibloc Injection (100 mg/ml).

Infusion rates of Brevibloc were controlled by an intravenous infusion pump capable of delivering a stable and sufficient volume to infuse the Brevibloc or placebo predictably and as scheduled. Infusion pumps were calibrated at the study sites before the study was initiated and checked throughout the study period to assure proper functioning.

Sample Collection:

Blood Samples:

Blood samples (1 ml each) to be used for determination of Brevibloc and ASL-8123 blood concentrations were collected just prior to initiation of the Brevibloc infusion during each of the five phases of the study. During Phases 0-IV, blood samples were also collected at 0, .25, .5, 1, 2, 3, 4, 5, and 6 hours; at 361, 362, 364, 366, 368, 370, 372, 374, 376, 378, 381, 384, 390, and 396 minutes; and at 7, 8, 10, 12, 14, 16, 20, and 24 hours following infusion initiation. During Phase V, blood samples were collected at 0.25, .5, 1, 2, 3, 4, 6, 12, 18, and 24 hours; at 1441, 1442, 1444, 1446, 1448, 1450, 1452, 1254, 1456, 1458, 1461, 1464, 1470, and 1476 minutes; and at 25, 26, 28, 30, 32, 34, 38, and 42 hours following infusion initiation.

In addition to the frequent monitoring of blood for Brevibloc concentration and that of its major metabolite (ASL-8123), the other major metabolite, methanol, and its subsequent metabolites were monitored. Methanolol is converted to formaldehyde which rapidly converts to formic acid. The formic acid formed can drive the equilibrium of bicarbonate towards formation of CO2 and H2O under severe conditions thus altering pH and bicarbonate concentrations.

During all five phases of the study, methanol, formate, and bicarbonate concentrations in plasma were determined just prior to initiation of the infusion and at 1, 3, 6, 12, and 24 hours following initiation of the dose. During Phase V, additional measurements of methanol and bicarbonate were taken at hours 36 and 42 while additional formate determinations were made at hours 34 and 42.

Urine Samples:

During each of the first hour phases, 14 cumulative urine samples were collected. The time periods, relative to infusion initiation, were -2-0, 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-10, 10-12, 12-14, 14-18, 18-22, 22-26, and 26-36 hours. Seventeen cumulative urine samples were collected during Phase V; the time periods were -2-0, 0-1, 1-2, 2-3, 3-4, 4-6, 6-12, 12-18, 18-24, 24-26, 26-28, 28-30, 30-32, 32-36, 36-40, 40-44, and 44-54 hours.

Analytical Methodology:

Because of the labile nature of the methyl ester of Brevibloc, particularly in blood, rapid extraction of Brevibloc and ASL-8123 was done at the clinical facility. (The extraction, therefore, is a likely source of error.) The firm stated that they processed samples as expeditiously as possible and frozen extracts were sent by air freight on dry ice to [redacted] for analysis. Analysis for Brevibloc and ASL-8123 in blood and urine samples were done using the standard methodologies described in Appendix A. Brevibloc was measured in blood using a GLC method and in urine using an HPLC method. The metabolite was measured in blood and urine using an HPLC method. In addition, Harris Labs also generated extracts of standard curves for the analysis. Results are presented in Appendix A.

Analysis of methanol and bicarbonate was done by [redacted]. Mean methanol concentrations in plasma did not exceed 5 mcg/ml, toxic concentrations are 1,000 to 3,000 mcg/ml, while normal levels are 0.1 to 2.0 mcg/ml. A complete description of the methanol validation, procedure and results are presented in Appendix A. All measurements of bicarbonate were found to be within normal ranges.

Analysis of formate were conducted at American Critical Care. None of the formate concentrations were found to exceed the reported normal endogenous range of 3.2-19.1 mcg/ml. A complete description of the method and its validation also is presented in Appendix A.

Statistical Methodology:

Due to the protocol restrictions between treatment phase and Brevibloc dosage, a typical crossover analysis was not applicable. Since there were no systematic differences among the pre-phase means, results over Phases I-IV for the 50, 100, 200, and 300 mcg/kg/min dosages were combined. For each dosage level, one-way repeated-measures analysis of variance models were then used to test for statistically significant differences among the means at the various time periods. If significant differences were observed, Dunnett's one-sided test was used to determine which subsequent means were significantly less than the pre-infusion mean.

Pharmacokinetic Methodology:

The pharmacokinetic analysis for this study was done as a two step process.

The first step utilized non-compartmental methods. Brevibloc steady-state blood concentrations (Css) were determined by dose and by subject as a mean of all Brevibloc blood concentration measurements taken between 1 hour after start of the infusion and the end of the infusion. T1/2 was determined by using a natural log-linear least squares analysis of the latest concentrations from a concentration vs. time profile.

Other parameters:

$$Cl = Ko/Css.$$

$$Vdss = \frac{(Ko)\,(Tinf)\,(AUCt\text{-}oo)}{(Css)\,(AUCO\text{-}oo)}$$

AUC was calculated by the trapezoidal rule and adding the ratio of the final plasma concentration divided by the terminal slope of the ln concetration vs. time curve.

Clearance of ASL-8123 was calculated employing the following equation:

$$CLe = (fm)\ Dose/AUCO\text{-}oo$$

where: fm is the fraction of the dose converted to ASL-8123, dose = (Ko)(Tinf), and AUC parameter is the area under the metabolite concentration vs. time curve from the start of the infusion to infinity. The value for fm was individualized by subject and dose. The fraction of the dose excreted in the urine as ASL-8123 was used.

The expected steady-state concentrations of ASL-8123 were estimated by:

$$Cssm = fm\ Ko/CLe \quad \text{or} \quad Cssm = AUCO\text{-}oo\ /\ Tinf$$

The frim reported that since the metabolite is eliminated in a mono-exponential fashion, the volume of distribution could easily be calculated as:

$$Vm = CLe\ /\ Kel$$

Where Kel is the elimination rate constant of metabolite.

Other parameters to be reported included: Cmax, Tmax, Cle, and t1/2.

Compartmental Methods:

See Figure 1 for a diagram of the model employed to describe the distribution of the drug and the principle metabolite.

Results:

Analytical methodology was valid.

Brevibloc Concentrations in Blood:

Blood concentrations vs. time estimates for each dose of esmolol and for each individual are presented in Tables 1 to 2. Mean plots of the data are presented in Figure 2.

Blood concentrations vs. time estimates of the major metabolite (ASL-8123) for each dose of esmolol also are presented in Tables 1 and 2. Mean plots are presented in Figure 3.

Blood concentrations of methanol rose to 30 to 76 mcg/ml (normal is 3 to 7 mcg/ml) and were well below the toxic concentrations reported to be in the range of 1,000-3,000 mcg/ml. Formate, an oxidation product of methanol, is responsible for the toxicity associated and normal concentrations are reported to be between 3.2 and 19.1 mcg/ml. The firm reported that none of the formate concentrations determined in the study were above the normal range. None of the bicarbonate measurements were found to be outside the normal range (23-32 mmol/L). Results are presented in Table 3.

Urine:

A summary of the mean amount and percent of the dose excreted for both drug and metabolite is presented in Table 4. The firm expressed the results as the hydrochloride salts. The firm adjusted for the difference in mol. weight in determining percent of the dose excreted. The overall mean percentages of the dose excreted for all doses were 0.76% and 73.2% for Brevibloc and ASL-8123, respectively.

Pharmacokinetic Analysis:
Non-compartmental:
Brevibloc Kinetics:

The steady-state concentrations (Css) determined from the samples taken between one hour and the end of the infusion are presented in Table 5 and a plot of the mean values is presented in Figure 4. A linear least squares regression of the relationship between Css and the dose resulted in a correlation coefficient of 0.819. The firm stated that this translates into a highly significant (p 0.001) linear correlation between dose and steady-stae blood concentrations for the dose range of 50-300 mcg/ml/min with an intercept not statistically significant different from zero. This does support the claim that the elimination of Breibloc was not saturable within the study range.

Half-life estimates, determined by linear regression of the terminal phase of the ln esmolol conc. vs. time curve, are presented in Table 6. The half-life estimate was not dose dependent and the overall mean half-life was reported to be 0.131 hours or 7.88 +/- 3.48 minutes.

Vdss were calculated as described previously and the results are summarized in Table 7. The overall mean +/- S.D. was 2.42 +/- 1.36 (n=30) L/Kg.

The mean TBC was 20.9 +/- 8.0 L/Kg/Hr and the results are presented in Table 8.

ASL-8123 Kinetics:

Infusion of esmolol was not long enough to have established steady-state of ASL-8123 during the 6 hour infusion periods. The mean concentration observed at 6 hours vs. dose by subject is plotted in Figure 5. Again, a linear least squares regression of these data resulted in a correlation coefficient of 0.937. This also translated into a highly significant (p 0.001) linear correlation between dose and six hour blood concentrations for the dose range 50-300 mcg/kg/min.

The predicted values for Css are reported in Table 9. A comparison of the predicted mean Css values with the mean maximum concentrations determined at six hours suggested that the ASL-8123 concentrations was at 68.5, 63.2, 73.7, 62.1, and 63% of the steady-state concentrations at 6 hours for the 50, 100, 150, 200, and 300 mcg/ml/min doses, respectively.

The half-life was calculated as ln2/slope of the natural log-linear plot. The determined half-life estimates are presented in Table 10. The terminal mean half-life was 4.03 +/- 0.56 hours and was not dose dependent.

The TBC for ASL-8123 was calculated from dose and AUC as previously described. The individual estimates are presented in Table 11 and the mean +/- S.D. was 0.08 +/- 0.016 L/Kg/Hr.

The vol. of distribution of the metabolite are summarized in Table 12 and the mean +/- S.D. was .485 +/- 0.085 L/Kg, (n=38).

The steady-state blood conc. of both esmolol and ASL-8123 apparently increase linearly with dose while the t1/2, Cl, and Vd for both compounds are apparently dose independent. The firm has constructed a table which presents the means, by dose, for esmolol and ASL-8123.

A summary of the PK parameters is presented in Table 13 for both Esmolol and for ASL-8123.

Model Dependent Kinetics:

The model, diagram presented in Figure 1, was employed to predict the distribution and elimination pharmacokinetics of Brevibloc. The firm has provided various parameters which indicate the suitability of the model and least-squares fitting procedure to determine the absence of systematic deviation in the plateau and biexponential disposition pattern of Brevibloc and essentially zero-order rise and subsequent monoexponential decline of metabolite concentrations.

The firm reported that the results yielded good to excellent correlation coefficients between the measured and fitted blood concentration profiles.

A summary of the NONLIN-generated least-square estimated parameters for Brevibloc and its metabolite as well as various secondary parameters for each of the 8 subjects is presented in Table 14.

Results suggested that esmolol distributes rapidly and appreciably into tissues. The mean intercompartmental clearance of 7.4 L/hr/kg is approximately 8.6 L/min., which is similar to cardiac output. The firm concluded that permeability of the drug into tissues is high since blood flow is the rate-limiting factor in the rate of tissue distribution of the drug.

The mean estimate of the Vc (1.9 L/kg) and Vss (3.3 L/kg) suggests a moderately large distribution space of the drug. This suggests that the drug may be appreciably bound to tissue or that there is a partitioning of the drug. The Vss value can be interpreted as a whole body tissue to blood distribution ratio and thus predicts that tissue concentrations at steady-state will average 3.3 times the blood concentration.

Total systemic clearance of esmolol was obtained at steady-state. The average value of 22.9 +/- 4.3 L/hr/kg is approximately 27 L/min which markedly exceeds both liver blood flow (1.5 l/min) and cardiac output (8 L/min.). This suggests that the high clearance of the drug is also a function of the ester hydrolysis and is consistent with biotransformation by 'non-specific enzymes' in blood and various body tissues. The rapid clearance and the large volume of distribution of esmolol account for the small time parameters of this drug. These parameters suggest that the major determinant of the duration of the drug concentrations in the body is the method of administration. With the cessation of the infusion of the drug, the mean t1/2 of the alpha phase was only 2.3 minutes, range 1.4 to 4.0 minutes, while the t1/2 of the beta phase was only 13 minutes.

The fitted parameters were employed to calculate Css for esmolol for each subject receiving each dose. The calculated Css are compared with the measured values presented in Table 15. The comparision also is a measure of the goodness of fit of the model to the data.

ASL-8123 Kinetics:

The propionic acid metabolite exhibited a small mean volume of distribution (Vm=0.44 +/- 0.09 L/kg) and a low mean clearance (Cl= 0.82 +/- 0.006 L/hr/kg). These results are consistant with the behavior of weak acids which are ionized at a physiological pH, and thus do not distribute to a great extent into the intracellular space. The result is that this drug is cleared to a large extent by the kidney (see kidney results where urine averaged 73.2 +/- 3.0% of the total dose). The Cle of ASL-8123 is moderate, 95 ml/min, and supports the premise that the clearance of this biotransformation product is

dependent upon the renal function of the patient and the subject.

Employing fitted parameters, the expected maximum concentrations of ASL-8123 at the termination of the infusion are presented in Table 16. The comparison of the measured values in the same table are in agreement.

Conclusion.

The parameters, in general, calculated by the non-compartmental and compartmental model methods are in good agreement. There appears to be more variability associated with pharmacokinetic parameters determined for esmolol when compared to the metabolite, however, this would be expected since the drug is eliminated so rapidly.

The pharmacokinetic analysis of the esmolol data demonstrated no dose dependency. There was an apparent linear relationship between dose and blood concentrations and the elimination parameters were not affected by alterations in the dose (range 50 to 300 mcg/kg/min). The very short T1/2B and the rapid clearance of the drug from the blood (mean of 27 L/min.) greatly exceeded both liver and cardiac output. This suggests that the drug is hydrolyzed extensively within the blood and surrounding tissues.

The pharmacokinetic analysis of the principle metabolite, ASL-8123 (propionic acid metabolite), demonstrated dose independent pharmacokinetics. The renal clearance of ASL-8123 is approximately 95. ml/min which is slightly less that the GFR in normal man, approximately 131 ml/min. This suggests that passive diffusion of the biotransformation product may play an important role in the renal excretion of the metabolite.

The firm determined that 73% of the dose was accounted for in the urine, while in another study, the overall percent accounted for in urine was 90%.

Study 2

Title: Pharmacokinetics Summary: Subacute human tolerance and beta blocking activity of ASL-8052 in normal volunteers.

Background: ASL-8052, esmolol, is a beta-adrenergic antagonist that, because of its short biological half-life, has been proposed to give physicians the flexibility of rapidly controlling not only onset, but also remission of therapeutic action. This study was partially designed to define the pharmacokinetics of ASL-8052 and its principle metabolite during and after a 48 hour infusion of ASL-8052 at 150 ug/min/kg.

Principle Investigator:
Kurt Schnelle, M.D.

Clinical Site: IPHAR, Munich, West Germany

Analytical Methodology: American Critical Care

ACC Study: #8052-81-03

Objective: The purpose of this report was to define the pharmacokinetic parameters of a short acting beta-adrenergic blocking agent, ASL-3052, and its major metabolite, ASL-8123.

Protocol: Eleven normal male subjects received ASL-8052 at an infusion rate of 150 ug/min/kg. The duration of the infusion was 6, 12, 24, 36, and 48 hours for subjects 201, 202, 203, 204-205, and 206-211, respectively. Blood samples were collected during and for 18 hours after the infusion. Complete urine also was collected during and up to 12 hours after infusion.

Sampling Process and Analytical Methodology:
Blood samples were collected and extracted by [redacted] and shipped to [redacted] for analysis. The processing was done according to the standard procedure presented in Appendix B. Standard curves also were prepared by [redacted] and shipped to [redacted] Urine samples were pooled for appropriate time periods, mixed, and an aliquot sent to [redacted] in the frozen state. Extraction and assay of urine samples, as well as preparation of standard curves for urine assays, were done at [redacted]

The GLC assay with electron capture detection of ASL-8052 was done according to the procedure presented in Appendix B. This assay is sensitive to [redacted] ng/ml with a coefficient of variation of 19.4% at that concentration. The coefficient is 12.8% and 11.5% for [redacted] ng/ml and [redacted] ng/ml, respectively. The linearity between [redacted] and [redacted] ng/ml is r = 0.983 with an n = 43. The assays for ASL-8123 were done using a HPLC method also presented in Appendix B. This assay is sensitive to [redacted] ug/ml with a coefficient of variation of 8 to 13%. The linearity was r = 0.997 with an n = 48.

Pharmacokinetic Analysis:

The firm reported that the steady-state concentration of ASL-8123 was calculated as a mean of the blood concentrations found between 17 hours and the end of tne infusion. The rate of elimination (B) was calculated by fitting the data on a semilog plot from stop of infusion until no more metabolite could be measured.

Total clearance was determined employing the following equations:

$$TC = \frac{Ko\ 60\ F\ f}{Css} \quad \text{or} \quad TC = \frac{KO\ 60\ F\ T\ 60\ f}{AUCO\text{--}\infty}$$

Where: F= 0.95 (mol. wt. ASL-8123/mol wt. of ASL-8052)
f= 0.88 (fraction of drug converted to ASL-8123 determined via urinary excretion)
T= time of infusion, hours
Css= steady-state concentration of ASL-8123 ug/ml (as described above)

The AUCO-oo for blood ASL-8123 was determined using the trapezoidal rule method for the time until the final sample at time t* was taken. The remaining portion of the AUC was estimated by dividing the plasma concentration at time t* (Ct) by B.

VdB was calculated as TC/B.

Results:

Analytical methodology was valid.

There is a major problem with the quantification of ASL-8052 in blood samples. The firm reported that because of inconsistant quantities of the internal standard for ASL-8052 found in different tubes for the standard curve, quantitation of ASL-8052 in the blood samples was not possible.. A rough estimate was made employing peak heights of the samples and comparing them to heights from the standard curves. This eliminates the use of internal standard and the values obtained are truely estimates. The results obtained from this study are not valid and merely suggest a trend and consequentialy, there will be no further review of the ASL-8052 data.

Results from the metabolite study are presented in Table 1, of Appendix C. These results determined a mean half-life of 243 minutes (+/- 13.7), mean total clearance of 118.1 (+/- 20.3) ml/hr x kg, mean steady-state blood concentrations was 65.1 (+/- 10.8) ug/ml, and a mean VdB of 0.68 (+/- .09) L/kg.

Urinary excretion of the two compounds are presented in Table 2. The results determined that 89.6% of the dose was accounted for in the urine of these subjects with 88.2% in the form of ASL-8052. For the 6 subjects receiving a 48 hour continuous infusion, the mean percentage of the dose excreted was 94.4, 88.3, and 90.1 for the 12-24, 24-36, and 36-48 hour periods, respectively.

The firm has admitted that a further study will be necessary to obtain valid pharmacokinetic information for the ASL-8052.

Conclusions: Results from the esmolol study are not valid, while the metabolite results merely suggest apparent PK parameters. The firm concluded that a further study was necessary to obtain valid pharmacokinetic information for the drug.

Study 3:

Title: Pharmacokinetics of ASL-8052 in Patients with Renal Impairment

Protocol Number: #8052-82-10

Investigators: Douglas Rollins, M.D., Ph.D.
Keith Tolman, M.D.
Wayne Border, M.D.
Martin Gregory, M.D.
Alfred Cheung, M.D.

Clinical Site: University of Utah
Abbott Research Center
Medical Center
Salt Lake City, Utah

Interim Summary: December 3, 1984

Design: This study is still ongoing and is to be performed in three healthy, male volunteers; three patients with mild renal impairment (24 hour creatinine clearance between 60-89 mL/min), three patients with moderate renal impairment (30-59 ml/min), and three patients with severe renal impairment (10-29 mL/min). The study design consists of a 4 hour Brevibloc (esmolol hydrochloride, ASL-8052) infusion at 150 ug/kg/min. Blood and urine samples are to be taken prior to, during, and after the infusion at appropriate intervals to allow accurate determination of the pharmacokinetic parameters of both Brevibloc and its acid metabolite, ASL-8123.

The firm has stated that enrollment into the study has been very slow. Of the seven normal subjects and the single patients who completed the study, no other adverse effects were noted by the investigator. The study is ongoing and attempts to enroll additional patients in the study are underway.

Study 4:

Title: Pharmacokinetics of Esmolol in Patients with Hepatic Disease

Protocol Number: #8052-84-50

Investiagators: Douglas Rollins, M.D. , Ph.D.
Keith Tolman, M.D.
Kenneth Buchi, M.D.

Institution: University of Utah
Abbott Research Center
Medical Center
Salt Lake City, Utah

Interim Summary: December 3, 1984

Study Design: This also is an ongoing study and is to be performed in none patients with documented liver disease (alcololic cirrhosis) and in three normal, healthy male volunteers. The study design consists of a four hour Brevibloc infusion at a rate of 200 ug/min/kg with blood and urine samples taken prior to, during, and after the infusion at appropriate intervals to allow accurate determination of the pharmacokinetic parameters of both Brevibloc and its acid metabolite, ASL-8123.

So far, three normal subjects and five patients have completed the study. An additional four liver disease patients will be studied. The firm stated that the analysis of the samples is in progress.

Study 5:

Title: A drug interaction study of esmolol HCl and digoxin in normal subjects.

Investigator: David Lowenthal, M.D.

Institution: Likoff Cardiovascular Institute of Hahnemann University
Hahnemann University
Philadelphia, Pa

Objectives: To evaluate the pharmacokinetic and pharmacodynamic interactions, if any, between iv infused Brevibloc and oral digoxin under steady-state conditions in normal, healthy, male subjects.

Study Design: Open label with a drug-free baseline control period, followed by Brevibloc, digoxin, and Brevibloc-digoxin study periods.

Study Population: Twelve healthy subjects, 22-33 years of age, were selected based upon acceptable and normal chemical and physical criteria.

Drug Administration: Brevibloc was administered by intravenous infusion. The dose of Brevibloc was titrated from 50-300 ug/min/kg and then maintained at 300 ug/min/kg. A loading dose (500 ug/min/kg) was given for one minute before each change in the dose during the titration. The total infusion time for Brevibloc was 6 hours. The loading doses were given in order to rapidly achieve the steady-state blood concentrations at each new dose level. The dose titration was continued until the maximum dose of 300 ug/kg/min was reached and this infusion rate was then maintained for 330 minutes. Digoxin (Lanoxicaps, Burroughs-Welcome) was administered orally. On the first day of digoxin administration each subject was given digoxin in two divided doses at twelve hour intervals and then a single dose in the morning on the subsequent study days. Doses were adjusted by subject to achieve a therapeutic serum concentration of .8-2 ng/ml. After study day 2, subjects were discharged from the institution with instructions for taking digoxin and making return visits for blood sampling. On the day before the last day of digoxin dosing, the subjects were admitted to the clinic and monitored for a 24 hour period. On the last day of digoxin dosing the subjects were administered Brevibloc and digoxin concomitantly and they remained in the clinic for 24 hours.

Study Medication: Brevibloc injection (Lot #933-37) was supplied by American Critical Care in 10 ml ampuls containing 250 mg of Brevibloc. Each 10 ml ampules contained:

Esmolol HCl	2.5 gm
Propylene Glycol USP	2.5 ml
Alcohol USP	2.5 ml
Water for inj. USP q.s. to	10 ml

Buffer with sodium acetate, USP, and glacial acetic acid, USP

Diluent for Brevibloc infusion was dextrose (5%) injection, USP.

Digoxin, in the form of Lanoxicaps, soft elastic gelatin capsules (0.2 mg, Lot #3F2864 and 0.1 mg, Lot #3J2889) was purchased from

Study 5:

Title: A drug interaction study of esmolol HCl and digoxin in normal subjects.

Investigator: David Lowenthal, M.D.

Institution: Likoff Cardiovascular Institute of Hahnemann University
Hahnemann University
Philadelphia, Pa

Objectives: To evaluate the pharmacokinetic and pharmacodynamic interactions, if any, between iv infused Brevibloc and oral digoxin under steady-state conditions in normal, healthy, male subjects.

Study Design: Open label with a drug-free baseline control period, followed by Brevibloc, digoxin, and Brevibloc-digoxin study periods.

Study Population: Twelve healthy subjects, 22-33 years of age, were selected based upon acceptable and normal chemical and physical criteria.

Drug Administration: Brevibloc was administered by intravenous infusion. The dose of Brevibloc was titrated from 50-300 ug/min/kg and then maintained at 300 ug/min/kg. A loading dose (500 ug/min/kg) was given for one minute before each change in the dose during the titration. The total infusion time for Brevibloc was 6 hours. The loading doses were given in order to rapidly achieve the steady-state blood concentrations at each new dose level. The dose titration was continued until the maximum dose of 300 ug/kg/min was reached and this infusion rate was then maintained for 330 minutes. Digoxin (Lanoxicaps, Burroughs-Welcome) was administered orally. On the first day of digoxin administration each subject was given digoxin in two divided doses at twelve hour intervals and then a single dose in the morning on the subsequent study days. Doses were adjusted by subject to achieve a therapeutic serum concentration of .8-2 ng/ml. After study day 2, subjects were discharged from the institution with instructions for taking digoxin and making return visits for blood sampling. On the day before the last day of digoxin dosing, the subjects were admitted to the clinic and monitored for a 24 hour period. On the last day of digoxin dosing the subjects were administered Brevibloc and digoxin concomitantly and they remained in the clinic for 24 hours.

Study Medication: Brevibloc injection (Lot #933-37) was supplied by American Critical Care in 10 ml ampuls containing 250 mg of Brevibloc. Each 10 ml ampules contained:

Esmolol HCl	2.5 gm
Propylene Glycol USP	2.5 ml
Alcohol USP	2.5 ml
Water for inj. USP q.s. to 10 ml	

Buffer with sodium acetate, USP, and glacial acetic acid, USP

Diluent for Brevibloc infusion was dextrose (5%) injection, USP.

Digoxin, in the form of Lanoxicaps, soft elastic gelatin capsules (0.2 mg, Lot #3F2864 and 0.1 mg, Lot #3J2889) was purchased from

Burroughs-Wellcome.

Brevibloc was administered by iv infusion. A pre-calibrated IMED volumetric pump (model No. 927 or 928) was used to predictably deliver a constant and pre-determined volume of Brevibloc as scheduled.

Digoxin was administered orally. Subjects were instructed to take the medication at home during study days 3 through 11 (digoxin stabilization period).

Sample Collection:

Blood samples were drawn before administration of Brevibloc at 4, 9, 14, 19, 24, 30, 60, 120, 240, and 360 minutes during infusion and a 1, 3, 5, 7, 9, 12, 15, 18, 21, 30, 60, 120, 240, and 360 minutes after discontinuation of Brevibloc. All samples were extracted at the study site and then stored in dry ice and flown to American Critical Care for further analysis.

Urine samples were scheduled to be taken before administration of Brevibloc at 0.5, 2, 4, and 6 hours during infusion and at 0.5, 2, 4, and 6 hours after discontinuation of Brevibloc infusion. Urine samples were packed with dry ice and sent by air freight to American Critical Care for further analysis.

Analytical Methodology: Presented in Appendix B.

Pharmacokinetic Calculations:

Css = average of the 60, 120, 240, and 360 minute concentrations during infusion of Brevibloc.

Cl = Ko / Css

T1/2 = ln2/the elimination rate constant (det. from linear regression analysis)

AUC0-6 for digoxin using the trapezoidal rule.

Brevibloc blood concentration-time data were also analyzed by non-linear regression analysis using the SAS methodologies and assuming linear kinetics. A weighting factor of 1/y2 and a one-compartment open model was used to fit the concentration versus time data.

Results:

Analytical method was valid.

Non-compartmental method:

All subjects completed the study. Individual blood concentrations for Brevibloc and its metabolite and serum concentrations for digoxin are presented in Appendix D. Complete urine samples were available only for Subjects 11 and 12, and all urine data are presented in Appendix D.

Pharmacokinetic parameters calculated using the non-compartmental method are presented in Table 1. The concentrations of Brevibloc after the administration of Brevibloc plus digoxin increased in 7 subjects while the concentrations decreased in 4 subjects. Means were not significantly different ($p|0.05$) between the two treatments with the mean

Css of 1.57 and 1.81 ug/ml following administration of Brevibloc and Brevibloc-digoxin, respectively.

Total body clearance of Brevibloc after Brevibloc-digoxin treatment were generally lower compared to those after Brevibloc alone. There were statistically significant differences ($p<0.05$) in the mean clearances between the two treatments. The mean total body clearances were 223 and 231 ml/min/kg after administration of Brevibloc and Brevibloc-digoxin, respectively.

The T1/2 of Brevibloc averaged 5.6 minutes after Brevibloc and 6.1 minutes after Brevibloc-digoxin treatments. There were no statistically significant differences ($p<0.05$) between the two treatments.

Compartmental Model

The post-infusion Brevibloc blood concentration vs. time data were described by a one term polyexponential equation following a 6 hour infusion of Brevibloc. The pharmacokinetic parameters calculated from the fitted data are presented in Table 2. The mean blood concentration-time plots for Brevibloc and its metabolie are presented in Figures 1 and 2, respectively.

The mean t1/2 of Brevibloc was 5.0 and 5.4 minutes after Brevibloc and Brevibloc-digoxin treatments, respectively. The results are very similar to the results presented above. Again, there were no statistically significant differences in the half-lifes between the two treatments.

TBC of Brevibloc calculated using the nonlinear computer fitting of the data were generally lower after Brevibloc-digoxin treatment. The table shows that the clearance varied considerably among subjects and between the two treatments, the difference between the means was not statistically significant (p 0.05). The mean clearance was 251 and 222 ml/min/kg after Brevibloc and Brevibloc-digoxin treatments, respectively. This compares favorably with the estimates reported above in the non-compartmental analysis.

The average volumes of distribution at the terminal phase were reported to be 1.97 and 1.60 L/kg following Brevibloc and Brevibloc-digoxin treatments. No statistically significant differences were reported when comparing the means of each treatment.

Urinary Recovery of Brevibloc and ASL-8123

Using the available data from only two subjects, the 'average' urinary recoveries of Brevibloc were 0.96% and 1.4% after Brevibloc and Brevibloc-digoxin treatments, respectively.(Tables 3 and 4) The parent drug was not determined in the urine 6 hours after termination of the infusion. The major fraction of the dose was recovered as the metabolite, ASL-8123. The recovery of the dose after 12-hours was 67.6% after Brevibloc and 61.8% after the administration of Brevibloc and digoxin. Plots are presented in Figure 3.

Blood Concentration and Half-life of the metabolite, ASL-8123:

There were no significant changes ($P|0.5$) in the t1/2 or in Cmax concentrations of the metaboite, ASL-8123, between Brevibloc and Brevibloc-digoxin treatments. The average max. conc. attained were 97.5 and 99.3 ug/ml following Brevibloc and Brevibloc-digoxin treatments, respectively.(Table 5) The average apparent elimination half-life, as determined by the non-compartmental method, averaged 3.5 hours after the Brevibloc treatment and 3.2 hours after the Brevibloc-digoxin treatment.

Digoxin Serum Concentrations:

The mean digoxin serum concentrations at different time points and peak concentrations during digoxin and Brevibloc-digoxin treatment are presented in Table 6. The average digoxin serum concentration-time profiles during the two treatments are presented in Appendix D.

The mean Tmax was reached at approximately 2 hours after either treatment. Differences between the mean Cmax were not statistically significant (p|0.5). The digoxin serum concentrations also were compared and only the 4-hour concentration was significantly different.

The AUC were calculated (0-6 hours) and are presented in Table 6. The mean AUC was significantly higher (p 0.5) after the Brevibloc-digoxin treatment than after digoxin treatment, averaging 11.4 ng x hr/ml after digoxin and 12.7 ng x hr/ml after Brevibloc-digoxin.

The estimated mean urinary recovery of digoxin was 27 and 33 % with and without Brevibloc, respectively. The urinary recoveries of digoxin are presented in Table 7.

Conclusion:

There does not appear to be any significant differences in the steady-state concentrations of Brevibloc between Brevibloc and Brevibloc-digoxin treatments indicating that the steady-state blood concentrations were not affected by digoxin. Clearance of Brevibloc did not appear to be affected by the co-administration of the digoxin. The large estimate of VdB for Brevibloc suggests a rapid elimination of Brevibloc. The limited urinary excretion data suggested that the parent drug was extensively biotransformed and eliminated extensively by the non-renal route.

There was a lack of statistically significant differences in the t1/2, Cmax of the metabolite, ASL-8123, between the two treatments. This suggests that the pharmacokinetic disposition is not influenced by the co-administration of digoxin.

There were no significant differences in digoxin peak serum concentration or in the time to reach the peak concentration. This suggests that Brevibloc did not affect the digoxin blood concentrations.

Labelling:

A copy of the pharmacokinetic labelling is presented in Appendix E. The firm has presented labelling which states that the pharmacokinetics of Brevibloc have been evaluated in patients with hepatic disease and end-stage renal disease. The claim states that the PK profiles were unchanged in these patients compared to those in normal subjects. I called the firm and talked to the Director of Regulatory Affairs, Lee Possley. I asked if they had submitted PK studies to substantiate the labelling claims. He stated that they had just completed the work on these studies and that the firm was reviewing the results. He made no mention of suppling the data to the Division of Biopharmaceutics at this time. Since the firm can not substantiate these claims at this time, the firm must delete this section from the PK and Metabolism section of the labelling.

Overall Conclusion:

1. The firm has defined the PK profile of the short acting beta-blocker, esmolol HCl and its weakly active biotransformation product, ASL-8123.

2. The firm must remove the following section in the pharmacokinetic and metabolism section of the labelling:

"The pharmacokinetics of Brevibloc have also been evaluated in patients with hepatic disease (cirrhosis) and end-stage renal disease. The pharmacokinetic profiles of esmolol were unchanged in these patients compared to those in normal subjects. The pharmacokinetics of the acid metabolite, however, were significantly different in patients with renal disease. The elimination half-life in these patients was increased about ten times that in normals, and the plasma levels were considerably elevated."

Recommendation:

The bioavailability study conducted by American Critical Care on its esmolol HCl IV injection, 100 mg/ml strength, has been found acceptable by the Division of Biopharmaceutics. However, the firm must delete the section in the PK and Metabolism section of the labelling which addresses the issue of pharmacokinetic profiles in patients with hepatic disease and end-stage renal disease.

The firm should be informed of the above recommendation and comment number 2.

Donald L. Heald 5-30-86

Donald L. Heald, Ph.D.
Pharmacokinetics Review Branch

RD Initialed by Mei Ying Huang, Ph.D.
FT Initialed by C.T. Viswanathan, Ph.D. SEE THE SUPERVISORY COMMENT ENCLOSED

cc: NDA 19-386 orig., HFN-110, HFN-226(Heald), Chron, Drug, Review, and Division Files

NDA 19386

Bio Portion

of MOR

THESE PAGES ARE FROM DR. LIEBERMAN'S MEDICAL OFFICER'S REVIEW OF NDA 19-386, BREVIBLOC.

BREVIBLOC® (esmolol hydrochloride) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.1.e. SPECIAL STUDIES: PHARMACODYNAMICS

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Williams, Roger, M.D.	8052-84-58	12 Subjects	Single-blind, placebo base line controlled determination of the relationship between duration of Brevibloc® infusion and onset and degree of beta blockade, at three dose levels.	Brevibloc® 100, 200, and 300 mcg/kg/min for 60 min at each dose level, with appropriate loading dose.	Assessment of beta blockade by determination of heart rate response to isoproterenol.	Brevibloc® reduced heart rate response to isoproterenol. Effect was rapid in onset and offset, and remained essentially level over each infusion period. There was no significant difference in heart rate reduction among the three dose levels. ADR's: Minor instances of bradycardia and hypotension were reported, as well as one instance of dizziness and increased PVC frequency.
Volume 3.12						
Deal, J., M.D.	8052-85-43	16 Subjects	Open-label, randomized, placebo base line controlled comparison of beta blockade potency and duration of Brevibloc® vs. oral and i.v. propranolol.	Brevibloc®: maintenance doses of 100, 200, 250, 300, 500, and 750 mcg/kg/min for one hour each, with appropriate loading doses. I.V. Propranolol: 99 mcg/min for one hour, with appropriate loading doses. Oral Propranolol: 40 mg tid x 2 days, then 80 mg tid x2 days. Later adjusted to 10, 20, and 40 mg respectively.	Measurement of heart rate response to isoproterenol challenge during each dosing regimen.	While Brevibloc® was significantly less effective, than i.v. or oral propranolol in attenuating heart rate response to isoproterenol challenge, the 300 mcg/kg/min dose of Brevibloc® produced an effect roughly equivalent to that of oral propranolol 10 mg tid. Steady state beta blockade was rapidly achieved with Brevibloc®, and offset was rapid following termination of 300 mcg/kg/min infusion. It was less rapid, although still time dependent, after 750 mcg/kg/min. ADR's: Frequent headache at high doses. Nausea and vomiting and symptomatic hypotension also at high doses. Non-symptomatic bradycardia (< 50 bpm) also observed.
Volume 3.13 (Medical)						
Volume 3.14 (Statistical)						
Iskandrian, A., M.D.	8052-82-19	19 Patients	Double-blind, cross-over comparison of the effects of Brevibloc® and propranolol on myocardial hemodynamics using radionuclide angiography.	Brevibloc®: Two minute loading dose of 500 mcg/kg/min, followed by continuous infusion of 300 mcg/kg/min until time of peak exercise. Propranolol: Four injections of 1 mg in 1 ml over 1 min, with 2 min observation period between doses 2 and 3.	Radionuclide angiography at rest and at peak exercise. Studies performed pre-drug, during Brevibloc®, and during propranolol, with 48 hour washouts between each. Blood chemistry, hematology, urinalysis, and study drug level determinations.	Brevibloc® and propranolol produced equivalent decreases in heart rate, ejection fraction double product, and cardiac index, both at rest and at peak exercise. ADR's: None reported.
Volume 3.15						

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.1.e. SPECIAL STUDIES: PHARMACODYNAMICS

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Ashoori, Joseph, M.D. Chicago, IL	8092-02-14	12 Patients	Open label evaluation of the hemodynamic effects of Brevibloc® in patients undergoing cardiac catheterization.	Brevibloc® loading dose 500 mcg/kg/min for 4 min followed by maintenance infusion of 300 mcg/kg/min for total infusion time of 20-27 min.	Baseline hemodynamics (e.g.: heart rate, systolic blood pressure, cardiac index, stroke-work index, and left ventricular ejection fraction) and remeasurement at infusion minute 16. Blood sample at minute 16 for Brevibloc® and metabolite level determinations.	This infusion level (300 mcg/kg/min) produced modest but statistically significant hemodynamic changes typical of beta-adrenergic blockade. Effects were rapidly reversed following infusion discontinuation, consistent with the short half-life of Brevibloc®.

Volume 3.16

BREVIBLOC® (esmolol HCl) INJECTION (NDA 19-386)
SUMMARY TABLE - CLINICAL STUDIES

E.1.c. SPECIAL STUDIES: PHARMACODYNAMICS

INVESTIGATOR / INSTITUTION	STUDY NUMBER	NUMBER OF SUBJECTS/ PATIENTS	DESCRIPTION	DRUG DOSAGE AND DURATION	TEST PARAMETERS FOR SAFETY AND/OR EFFICACY	RESULTS
Greenspon, Alan, M.D. Philadelphia, PA	8092-82-13	17 Patients	Open label study of the electrophysiologic effects of Brevibloc® administered by I.V. infusion to patients hospitalized for routine diagnostic electrophysiologic testing.	Loading dose of 500 mcg/kg/min three to five minutes followed by maintenance infusion of 300 mcg/kg/min for total infusion time of 15 to 45 min.	Electrocardiographic recordings and determinations of sinoatrial nodal function, atrial conduction time and atrial refractoriness, AV node and His-Purkinje system function, ventricular function, and retrograde conduction; 12-lead ECG; hematology; SMA-12; serum electrolytes and urinalysis.	During Brevibloc® infusion, these modest but statistically significant changes were noted: 1) heart rate decrease 2) SA node recovery time prolongation 3) Prolongation of AH interval during atrial pacing 4) Increase in anterograde Wenckebach cycle length. Thirty minutes post-infusion several significant changes from baseline were observed: 1) increase in heart rate, 2) shortened sinus- and corrected sinus node recovery time, 3) shortened paced AH interval, 4) shortened AV node effective refractory period at 470- and 600 msec, 5) shortened atrial effective refractory period during 600 msec pacing. ADR's: hypotension, diaphoresis, atrial flutter, chest tightness, pressure, bradycardia, vasovagal reaction, vomiting. Only vomiting was attributed to Brevibloc®.
Volume 3.17						
Kaplan, Asst., M.D. New York, NY	8092-82-22	20 Patients	Double-blind, randomized, placebo-controlled study of the effects of Brevibloc® on hemodynamics in anesthetized patients post-intubation.	Brevibloc® infused at 100-, 200-, and 300 mcg/kg/min for ten min at each level, with each level preceded by a 500 mcg/kg/min loading dose for 1.5 min; or placebo.	Hemodynamic measurements pre-induction, post-intubation, at the conclusion of each dosing interval, and at 15- and 30 min post-infusion.	Brevibloc® was hemodynamically safe at all three dosing levels in this patient group anesthetized with fentanyl, oxygen, and pancuronium. ADR's: One patient receiving placebo developed bradycardia and low cardiac index.
Volume 3.18						

Table B_1

Pharmacokinetics in Normal Subjects

Study Number	Dosages Given mcg/kg/min (duration)	Number of Volunteers	Pharmacokinetic Results
Pharmacokinetics			
8052-81-01 (Vol. 3.2, page 1)	10, 40, 100, 150, 200, 300, 450, 650 (1.0 hr each)	6	Blood level proportional to dose. Estimated apparent half-life less than 10 minutes. Large total clearance >12 L/hr/kg.
8052-81-02 (Vol. 3.3, page 1)	50, 150, 400 (2.0 hr each)	8	Blood levels proportional to dose. Data fit 2 compartment model. Pharmacokinetic parameters defined for 400 mcg/kg/min dosage.
8052-81-03 (Vol. 3.5 page 1)	150 (6-48 hours)	8	Brevibloc data not retrievable. Acid metabolite pharmacokinetics defined. Urinary excretion measured.
8052-82-09 (Vol. 3.8, page 1)	50, 100, 200, 300 (6.0 hr each) 150 (24 hours)	8	Complete pharmacokinetic analysis of Brevibloc and acid metabolite. Demonstrates linear kinetics.
Pharmacodynamics			
8052-84-58 (Vol. 3.12, page 1)	100, 200, 300 (1.0 hr each)	12	Confirmed theoretical dosing scheme. Steady-state levels proportional to dose. Rapid elimination postinfusion shown.
8052-83-43 (Vol. 3.13, page 1)	100, 200, 300 (1.0 hr each) 250, 500, 750 (1.0 hr each)	8	Steady-state level measured and found proportional to dose. Rapid elimination postinfusion shown.
Drug Interaction			
8052-83-38 (Vol. 3.19, page 1)	300 (6 hr)	10	Steady-state of Brevibloc elevated in some subjects during morphine administration. All other kinetic parameters unchanged.
8052-83-39 (Vol. 3.22, page 1)	300 (6 hr)	12	No effect of digoxin of Brevibloc kinetics.

Table b_2

Pharmacokinetics in Disease States*

Study Number	Volume	Page	Patient Type	Dosages Given mcg/kg/min Duration	Volunteers
8052-82-10**	3.10	208	Renal Impairment	150 (4.0 hrs)	12
8052-83-50**	3.10	211	Hepatic Disease	200 (4 hrs)	12
8052-82-13	3.17	1	Organic Heart Disease	300 (<1.0 hr)	17
8052-82-14	3.16	1	Organic Heart Disease	300 (15 min)	12
8052-82-15	3.15	1	Coronary Artery Disease	200 (<1 hr)	15
8052-82-21◆	3.28	1	Coronary Revascularization	100 or 200 or 300 (7 min each)	42
8052-83-25◆	3.18	1	Coronary Revascularization	100, 200, 300 (10 min each)	20
8052-83-44◆	3.29	1	Non-cardiac Surgery	100 or 200 or 300 (10 min each)	40
8052-83-45◆	3.30	1	Non-cardiac Surgery	100 or 200 or 300	31

* Breviblec steady-states were measured in all studies and shown to be proportional to dosage in studies where multiple dosages were given. The rapid elimination of Breviblec after discontinuation of infusion was documented in each study.

** Studies in progress.

◆ Anesthesia studies.

3. Description of Dosage Form and Quantitative Composition

Brevibloc® injection is a sterile, non-pyrogenic solution for intravenous infusion, supplied in 10 mL Type I glass ampuls in two strengths: 1.0 g/10 mL (100 mg/mL) and 2.5 g/10 mL (250 mg/mL). The two strengths are identical in composition with respect to both active and inactive ingredients and differ only with respect to concentration as shown below:

	1 gram 100 mg/mL 10 mL ampul	2.5 gram 250 mg/mL 10 mL ampul
Active Ingredient		
Esmolol Hydrochloride	1.0 g	2.5 g

C. Overview of Pharmacokinetics/Pharmacodynamics/Safety

A series (approximately 40-50 studies) of phase I and II studies defined the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of esmolol and provided initial evidence of efficacy. An overview of the studies, investigators, purposes, doses, duration of the studies and results can be found in Tables A, B_1, B_2 and Table C. Of these studies, approximately 17 were primarily related to pharmacokinetics in normal subjects and in diseased subjects, 4 were related to drug interactions, 7 were related to pharmacodynamics, 7 were related to safety including tolerance and venous irritation potential and 1 evaluated $beta_1$ selectivity in asthmatic patients. Clinical pharmacology studies were arranged by the sponsor into two major categories:

1. Special Studies
   a. Safety (Tolerance)
   b. Pharmacokinetics (PK)
   c. Pharmacodynamics (PD)
   d. Drug Interaction Studies
   e. Other Studies

2. Dose Ranging Studies
   a. SVT
   b. Perioperative

In essence, these studies purport to show that:

1. Esmolol is reasonably well tolerated in normal subjects and patients within the dose range evaluated.

2. Esmolol is rapidly metabolized by blood and tissue esterases.

3. Esmolol has a plasma terminal half life (t 1/2) of about 9 minutes.

4. Esmolol acts a true "beta blocker in man.

5. Steady-state blood levels of esmolol and relatively stable beta blockade are attained with an initial loading dose followed by a maintenance dose.

6. A dose-response relationship or trend is demonstrated in patients with SVT in controlling ventricular rate and in perioperative (anesthetized) patients in modulating hypertension and tachycardia.

Medical Reviewer's Note

Due to insufficient information and lack of specific date, several of the above conclusions were not clearly supported by the NDA (especially #3 and #6). Therefore, we have asked the sponsor to address these issues which relate to the pharmacokinetic (PK) and pharmacodynamic (PD) data. The specific deficiencies or problems are identified in the appropriate sections (overview summary for the respective studies. These include:

(1) Data supporting the computer model for first order kinetics for the elimination half-life.

(2) Data clarifying the relationship of esmolol dose to response as measured by % inhibition of the response to isoproterenol.

What is the correct dose response curve?

(3) Data supporting the sponsor's claim of a dose response effect in the perioperative setting.

The sponsor's response to the first two issues are found in the Addendum to the Clinical Pharmacology Section at the end of the entire section. The analysis re issue #3 is found in the section re dose ranging studies.

1. Special Studies

a. Safety Studies in Normal Volunteers

1. Tolerance Studies

Twenty-five healthy, normal young adult male volunteers were evaluated in three single blind placebo controlled human tolerance studies (8052-81-01/02/03) with IV infusions of esmolol conducted by Dr. K. Schnelle. The pharmacokinetic and pharmacodynamic aspects of these studies will be discussed elsewhere under the appropriate section. Table A summarizes the drug schedules and test parameters for safety/efficacy. The data obtained from these studies indicated that esmolol was well tolerated at all the infusion rates and duration studied (up to 650 mcg/kg/min for 1 hour, up to 400 mcg/kg/min for 2 hours and up to 48 hours 150 mcg/kg/min). The side effects reported during these studies consisted of: fatigue, headache, facial warmth, rhinitis, diarrhea, and inability to read due to heavy eyes. The maximum plasma concentration of methanol resulting from metabolism of esmolol was 9 mcg/ml, which approximates the endongeous range and is about 2 orders of magnitude below any level associated with toxicity. No clinically significant effect on laboratory parameters monitored were noted. In summary esmolol when administered to normal male volunteers in doses ranging from 10 to 650 mcg/kg/min for periods ranging from 1 to 48 hours was well tolerated and showed dose dependent beta blockade of the tachycardia, increase in SBP, and decrease in DBP induced by an isoproterenol challenge.

2. Irritation Potential Studies

Three additional studies (8052-82-12, 8052-83-24, and 8052-83-46) were conducted to evaluate the venous and perivascular irritation potential of esmolol. The first study 8052-82-12 employed esmolol 10 mg/ml whereas the other two studies used a esmolol concentration of 20 mg/ml. All three studies were associated with a significant incidence of venous and perivascular adverse effects including pain, swelling, soreness, itching, burning, erythema, numbness and induration. In contrast to the first study (in which only a minority of subjects [3 out of 19] were terminated due to local infusion site reactions), the other two studies resulted in a majority of subjects being prematurely terminated due to severe local infusion site reactions. Phlebitis and thrombosis of the infused vein was noted in 8 out of 9 subjects in the third study. These studies led to the guideline that the concentration of esmolol should not exceed 10 mg/ml. In addition, a transient but statistically significant reduction in SBP was noted at 20 minutes and 12 hours after the start of the esmolol infusion.

3. Beta 1-Selectivity Study in Asthmatic Subjects 8052-83-34

Study Objective

The objective of this study was to compare the safety of esmolol with placebo in patients with asthma by examining the effects on airway function, responsiveness to dry air induced bronchial constriction, and responsiveness to isoproterenol-induced bronchial dilation.

Patients

Ten patients with mild asthma entered and completed the study. Data from all 10 patients were acceptable for analysis of pulmonary function. The safety evaluation was based on all 10 patients, but one patient had prestudy laboratory data excluded from analysis. Under a protocol amendment, 6 of the 10 patients were also studied to compare the effects of propranolol vs placebo.

Study Design and Treatment Plan

This study was a double-blind, randomized, placebo controlled crossover study. Following baseline pulmonary function testing, esmolol or placebo was administered by continuous intravenous infusion in a titration phase and a maintenance phase. The infusion was titrated stepwise to dosages of 100, 200 and 300 mcg/kg/min; each dose was preceeded by a loading dose of 500 mcg/kg/min for 1.5 minutes. The infusion was continued to the maxmimum dose. The patient was entered into a maintenance phase at a dose of 300 mcg/kg/min for 30 minutes. Throughout the dry air and isoproterenol dose response periods, the infusion of esmolol or placebo was continued at the 300 mcg/kg/min dosage. Additionally, propranolol was administered by bolus injection to 6 of the 10 patients after completion of the entire esmolol-placebo phase in a dosage of 1-5 mg.

Efficacy Evaluation

The primary endpoints assessed included pulmonary function test, plethysmography, blood chemistry, hematology, urinalysis and vital signs.

Results

During the titration and maintenance periods, no significant differences were found between the effects of esmolol and placebo on airway function, in the dry air test however esmolol when compared to placebo lowered the ventilation producing a 100% increase in specific airway resistance (PV-100). This effect was small in magnitude - PV-100 was 46.3 $\pm$ 1.7 during esmolol and 50.2 $\pm$ 2.7 during placebo. This suggested a slightly enhanced bronchomotor sensitivity to the stimulus of dry air during esmolol infusion. Esmolol inhibited bronchomotor responsiveness to isuprel in comparison to placebo but only after the first meter dose of isuprel. The difference between esmolol and placebo and specific airway

resistance (sRaw) after the first isuprel dose was also small, sRaw was 6.77 ± 1.2 during esmolol and 5.7 ± 1 during placebo. Esmolol also had a greater than 75% reversal of induced bronchial constriction after the first dose of isuprel. In the propranolol part of the study, 2 of the 6 patients had marked symptomatic bronchial constriction after 1 mg of propranolol. A third patient had a clinically significant change in sensitivity to dry air; PV-100 after propranolol was 26 liters per minute compared to 45.3 liters per minute after placebo.

Adverse Drug Effects

5 of the 10 patients had adverse effects during esmolol infusion. The adverse effects consisted of hypotension (2 instances), dizziness (2 instances), anxiety, headache and slight bronchial constriction except for headache which occurred during the post infusion period. All adverse effects occurred during the maintenance period at the 300 mcg/kg/min dosage period. All adverse reactions were described as mild and none required discontinuation of esmolol infusion. In conclusion, esmolol in the doses administered produced slight but statistically significant effects on bronchomotor response to dry air and isuprel in patients with mild asthma. Propranolol in the same patients, produced more profound effects: marked symptomatic bronchoconstriction in 3 of the 6 patients accompanied by an increase in the specific airway resistance without dry air provocation in two of the six patients. Since the number of patients studied was relatively small no absolute conclusions about the overall safety of esmolol in patients with asthma can be drawn. These studies are of particular relevance to the clinical efficacy trials since the loading dose titration schedule and maintenance doses were almost identical to the treatment schedule employed in the clinical efficacy trials involving patients with SVT and in the perioperative setting.

CLINICAL PHARMACOLOGY

1. Special Studies

b. Pharmacokinetics

Overview Summary

The pharmacokinetics of esmolol and its chief metabolite (ASL-8123) have been deduced from a series of clinical studies in normal, healthy human volunteers (8052-81-01/02/03/09) (Tables A, B_1).. Additional data has been obtained from patients with various disease states and in patients undergoing surgical or other medical procedures (see Tables B_2 and C). These studies have provided the basis for the dosage regimen developed and subsequently employed in the controlled clinical trials (see Table D). In addition, a computer modeling system was developed to predict blood levels based on varying infusion regimens. (For complete details see Appendix 1A.) As a result of this modeling scheme, it was deduced that the optimum regimen would require an initial loading dose followed by a maintenance dose in order to rapidly

achieve the desired steady state blood levels. Based on the results of the studies summarized in the preceeding tables, the following conclusions about the pharmacokinetics of esmolol and its acid metabolite are purported by the sponsor:

1. Esmolol displays linear kinetics over the dose range of 50-300 mcg/kg/min.

2. It has a terminal half life (t1/2) of about 9 minutes.

3. Clearance is primarily the result of hydrolysis of its ester bond in blood and tissues and is not significantly dependent on blood flow as its clearance exceeds cardiac output.

4. The majority of esmolol is excreted changed (as the acid metabolite).

5. The acid metabolite formed by hydrolysis of esmolol is cleared by renal excretion and has a terminal half life of almost 4 hours (3.7 hours).

6. Therefore the rapid metabolism of esmolol allows blood levels and beta blocking activity to be quickly altered or eliminated by changes in the infusion rate of the drug.

One important technical consideration relates to the fact that blood sampling does not stop the hydrolysis of the drug and so rapid inhibition and denaturation of the esterase followed by separation of the drug and metabolite was required. This was solved by partial inhibition of the esterase by collection of samples in sodium flouride and rapid denaturation and separation of the drug and metabolites by the addition of blood into methylene chloride.

Medical Reviewer's Note

Due to lack of data points and incomplete graphs, it is not possible to conclude that esmolol's elimination half-life follows first order kinetics. The data presented implies that the time to reach steady state depends on the infusion rate. Hence the following data plots have been requested for studies 01,02,09:

1. A plot of the individual subjects (log blood conc vs time) for esmolol, acid metabolite and methanol.

2. Analysis of above to check for model fit.

3. Data re infusion studies for 100, 250, 500 and 750 mcg/kg/min.

4. Details of the analytical sensitivity for esmolol.

Note:

The sponsor's response to this request can be found in Appendix 1C of the Addendum to the Clin. Phar.

Results of Specific Studies

Studies 01, 02, 03, 09

[Initial Studies and Computer Modeling]

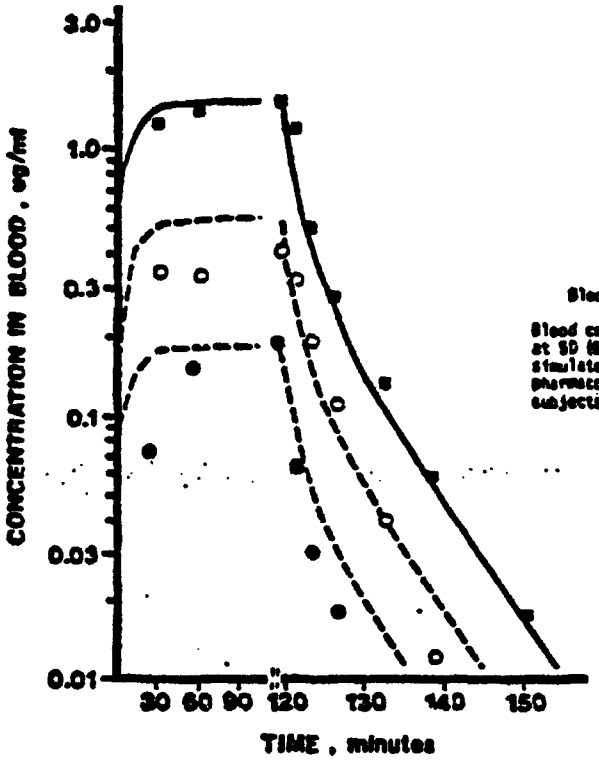
The initial clinical study (8052-81-01) demonstrated that steady state concentrations of esmolol were proportionally linear with the dosage administered over the range of 40-650 mcg/kg/min and that the drug had a elimination half life of less than 10 minutes. This data was obtained in 6 normal male subjects who received the following 1 hour infusions of esmolol at 40, 100, 200, 300, 450 and 650 mcg/kg/min. Basic pharmacokinetic parameters of esmolol and ASL 8123 were then established in study 02 (8052-81-02) using dosages of 50, 150, and 400 mcg/kg/min administered for 2 hours. In this study 8 normal male subjects were each infused for 2 hours at three different dosages of esmolol. However, only the 400 mcg/kg/min dosage resulted in sufficient esmolol blood level data to allow standard pharmacokinetic modeling. The data were fitted to a two-compartment model and the following parameters were established for esmolol:

Steady state concentration 400 mcg/kg/min:	1.59 mcg/ml
Half life of distribution:	2.03 minutes
Half life of elimination:	9.19 minutes
Volume of distribution:	3.43 liters/kg
Total body clearance:	17.1 liters/hr/kg

Additionally, the data obtained at three dosage levels for the acid metabolite ASL-8123 were fitted to a one-compartment model and its pharmacokinetic parameters were established as follows:

Half life of elimination:	223 minutes
Volume of distribution:	0.41 liters/kg
Total body clearance:	0.077 liters/hr/kg

These pharmacokinetic parameters were then used to simulate blood concentration curves for the 50 and 150 mcg/kg/min dosage, and the actual data compared very well (according to the sponsor) with the simulated values as shown in the following figure.



Blood Concentration vs. Time Profile

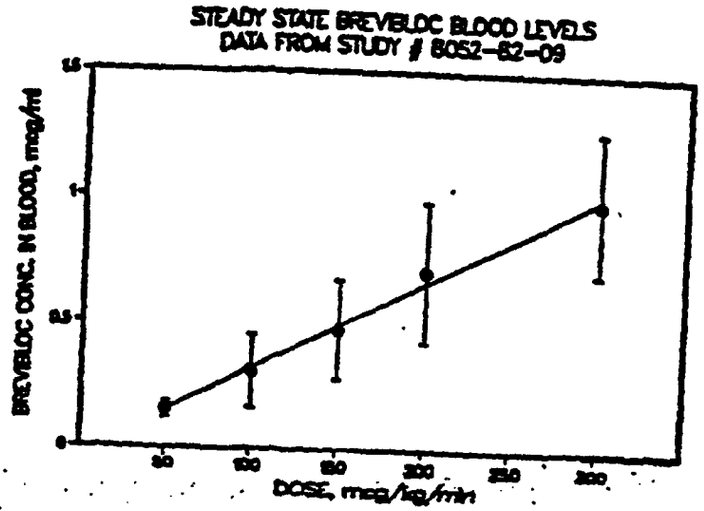
Blood concentrations versus time profile of Brevibloc at 50 (●), 150 (○), and 300 (■) mcg/kg/min and simulated blood levels (dashed lines) based on average pharmacokinetic parameters obtained from eight normal subjects (Study 8052-81-02).

An additional study (8052-81-03) was designed to further define the kinetics of esmolol and ASL-8123. This was a study in 11 normal male subjects who received a single infusion of esmolol. Subjects received 6, 12, and 24 hour infusions, or 36 hour infusions or a 48 hour infusion. Due to difficulties in the extraction procedure at the clinical site, the only retrievable data was for the acid metabolite, ASL-8123. It was shown that the elimination half-life, volume of distribution, and total clearance of metabolite were 222 minutes, 0.69 liters/kg, and 0.118 liters/hr/kg, respectively. Urine analysis results showed that 1.4% of the dose administered during the 48 hour infusion was excreted as unchanged drug. However, almost 90% of the dose was accounted for in the form of urinary ASL-8123. These results were similar to animal data which showed around 98% of the dose was excreted as esmolol or ASL-8123 in the urine and around 4% of the dose in the feces.

Hence the data from these early studies were used to model blood levels for various dosing regimens. Two criteria were used in design of dosing regimens. First, the infusion rate should remain below the maximum 650 mcg/kg/min dosage which was shown to be well tolerated in the initial clinical study and secondly, steady state drug levels should be established rapidly enough to allow a decision to be made within 5 minutes to go to a higher dosage (if inadequate response) or remain at the current dosage (if adequate response). Computer simulations (Study 8052-81-02) of blood level profiles resulted in the dosage regimens employed in subsequent controlled clinical studies. (See Appendix 1A)

[Additional Studies and Conclusions]

Another detailed study (8052-82-09) was conducted to establish the pharmacokinetics of esmolol and its acid metabolite in normal subjects. The study consisted of 5 phases: 4 phases were randomized and consisted of 6 hour esmolol infusions at 50, 100, 200, and 300 mcg/kg/min. The fifth phase for all subjects was a 24 hour infusion of esmolol at 150 mcg/kg/min. Data from the study were analyzed by subject using (1) models of independent methods to confirm that linear kinetics were followed and also by (2) comprehensive modeling of both drug and acid metabolite data for all 5 doses simultaneously. The linearity of Brevibloc blood levels vs dosage was demonstrated (see the accompanying figure) and complete pharmacokinetic results for esmolol and ASL-8123 are summarized in the following table.



Summary of Pharmacokinetic Parameters
for Breviblec and ASL-8123
(Study #8052-82-09)

Breviblec Parameters:	
Central Volume of Distribution:	1.9 L/kg
Tissue Volume of Distribution:	1.4 L/kg
Steady-State Volume of Distribution:	3.3 L/kg
Intercompartmental (Distribution) Clearance:	7.4 L/h/kg
Formation Clearance of ASL-8123:	15.7 L/h/kg
Total Clearance:	22.9 L/h/kg
Mean Residence Time:	8.3 minutes
Distribution Half-Life:	2.3 minutes
Elimination Half-Life:	13 minutes
Fractional Metabolism:	0.73
ASL-8123 Parameters:	
Volume of Distribution:	0.44 L/kg
Renal Clearance:	0.08 L/h/kg
Elimination Half-Life:	3.7 hours

The overall results of this study are as follows:

1. Brevibloc distributes rapidly and significantly into tissues. Since the intercompartmental clearance is approximately 8.6 liters/minute (which is similar to cardiac output), the permeability into tissues is high and blood flow is probably the rate-limiting factor in tissue distribution.

2. The central (V_c equals 1.9 liters/kg) and total (Vss equals 3.3 liters/kg) volume of distribution of the drug are moderately large. This is consistent with the high permeability rate and is indicative of significant tissue binding. Extrapolating from the Vss value, it can be predicted that tissue concentrations at steady state will average 3.3 times the blood concentration.

3. The total clearance of esmolol was found to be 22.9 L/hr/kg or roughly 27 liters/min which clearly exceeds both liver flow (1.5 L/min) and cardiac output (8 L/min). The high clearances and a pathway which mainly involves formation of the propionic acid metabolite by ester hydrolysis is consistent with biotransformation by nonspecific enzymes in blood and various body tissues. Methanol, the other metabolite formed from esmolol metabolism, does not appear to significantly accumulate (studies 8052-81-03 and 8052-82-09).

4. The mean residence time of 8.3 minutes suggest that the major determinant of the duration of drug concentration in body will be the duration of administration. The disposition occurs with an initial (alpha) half life of 2.3 minutes and a slower (T1/2 beta) half life of 9 minutes. The T1/2 beta is the dominant phase of elimination with a very small variation among the subjects studied (study 8052-82-09).

5. In contrast, the acid metabolite (ASL-8123) shows a small volume of distribution and low total body clearance. The renal clearance of ASL-8123 is moderate, (about 95 ml per minute,) and probably will be strongly dependent upon the renal function of the patient or subject.

Steady State Levels of ASL-8123

Two studies (8052-81-03 and 8052-82-09) had sufficiently long infusion rates to be able to establish steady state parameters of the acid metabolite. Both long term infusions were at the 150 mcg/kg/min dosage. In these studies mean steady state ASl-8123 levels were found to be 65.1 mcg/ml and 64.3 mcg/ml. In general the maximum concentrations were proportional to esmolol dose.

Steady State Levels of Brevibloc in Disease States

In addition to these key pharmacokinetic studies just described, additional blood levels have been determined from a number of studies to check for consistencies of these parameters in various disease states. In all of these studies, the dosing regimens involved loading doses of 500 mcg/kg/min for various lengths of time followed by maintenance doses of the desired rates. Study 8052-81-58 confirmed that the approximate steady state levels were obtained within 5 minutes using this scheme. The data from studies in patients with hepatic dysfunction and renal insufficiency are not available as yet for analysis (studies incomplete).

Steady State Brevibloc Levels (Venous and Arterial)

The steady state venous and arterial esmolol levels from the various individual studies are provided in the following tables and summarized in graphic form in the following figures. These studies reinforce the previous findings that the steady state esmolol blood levels are proportional to dose.

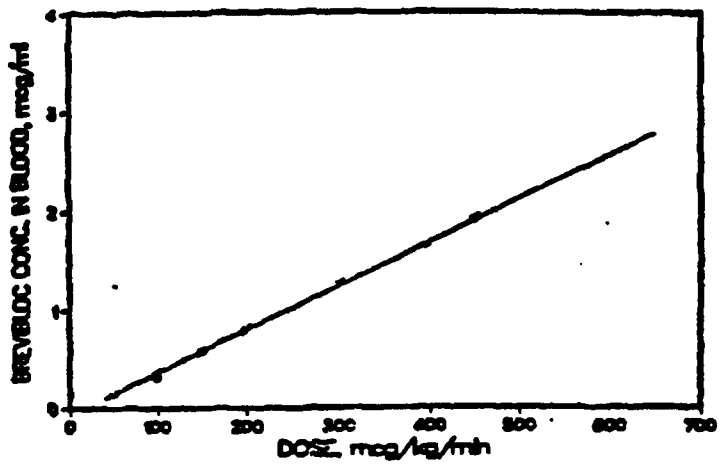
Mean (± SD) Brevibloc Levels in Venous Blood

Study #	Dosage (mcg/kg/min)							
	50	100	150	200	250	300	500	750
8052-81-01*	—	0.464±0.170	—	0.977±0.201	—	1.31	—	—
8052-81-02**	0.164±0.068	—	0.369±0.204	—	--	—	--	—
8052-82-09	0.158±0.032	0.312±0.141	0.479±0.195	0.711±0.277	—	0.993±0.280	—	—
8052-82-13	—	—	—	—	—	0.842±0.681 1.01±0.399	—	—
8052-82-14-01	—	-	-	—	—	0.581±0.183	—	—
8052-82-15	-	-	—	0.533±0.289	—	--	-	—
8052-82-38	—	—	—	-	—	1.61±0.768	—	—
8052-82-39	—	--	—	—	—	1.57±0.658	—	—
8052-82-43	— —	0.336±0.208 0.576±0.291	— —	0.820±0.429 —	— 1.32±0.615	1.09±0.524 —	— 3.32±1.24	— 5.47±2.43
8052-84-38	—	0.401±0.206	—	1.01±0.319	—	1.69±0.611	—	—

* Steady-state levels were also measured at dosages of 40, 450, and 650 mcg/kg/min and the mean ± S.D. were found to be 0.202 ± 0.088, 1.92 ± 0.30, and 2.9**, respectively.

** Steady-state levels were also measured at a dosage of 400 mcg/kg/min and the mean ± S.D. was found to be 1.5 ± 0.665.

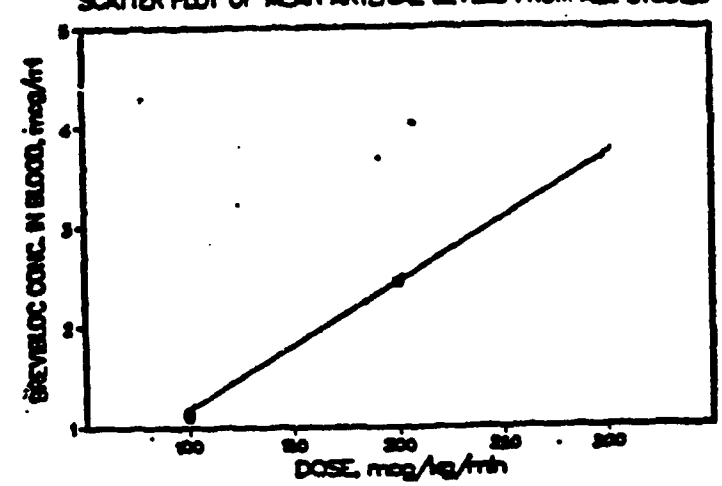
STEADY STATE BREVIBLOC BLOOD LEVELS
SCATTER PLOT OF MEAN VENOUS LEVELS FROM ALL STUDIES



Mean ± SD Brevibloc Levels in Arterial Blood Dosage (mcg/kg·min)

Study #	100	200	300
8082-82-14	---	---	3.93 ± 1.35
8082-82-21	1.20 ± 0.363	2.44 ± 0.517	3.63 ± 1.91
8082-83-25	1.25 ± 0.249	2.68 ± 0.864	4.19 ± 1.13
8082-83-44	1.09 ± 0.410	2.21 ± 1.13	3.08 ± 2.13
8082-83-45	1.13 ± 0.378	2.69 ± 1.01	3.76 ± 1.57

STEADY STATE BREVIBLOC BLOOD LEVELS
SCATTER PLOT OF MEAN ARTERIAL LEVELS FROM ALL STUDIES



Elimination of Brevibloc and Plasma Half Life

The rapid elimination of esmolol was also monitored in these studies by sampling 30 minutes after termination of the infusion. The results consistently showed that very low levels were present 30 minutes after termination of infusion (these were usually not quantifiable). Estimated half lives (which were based on a limited number of data points) were reasonably consistent with an estimation of less than 10 minutes whether in normal subjects or the diseased states previously discussed. (See Appendix 1C)

Protein Binding of Brevibloc and ASL-8123

In vitro studies were conducted to measure the protein binding of esmolol and its acid metabolite. The results as noted in the accompanying figure show only moderate binding of esmolol and negligible binding of ASL-8123.

Protein Binding of Brevibloc and ASL-8123

Species of Protein Solution	% Brevibloc Bound	% ASL-8123 Bound
Dog Serum	38.3	2.0
Human Serum	56.2	7.0
Human Albumin	24.5	4.3
Human AAG	21.3	4.4
Mouse Serum	43.8	---
Rabbit Serum	42.0	8.7
Rat Serum	44.3	8.4

Summary and Conclusion

Esmolol has a very short duration of pharmacological action in vivo because of its rapid metabolic biotransformation. Animal studies have shown that this rapid inactivation occurs by hydrolysis of the methyl ester group in esmolol to the corresponding carboxylic acid (ASL-8123) via blood and tissue esterases. The drug must be administered by the IV route and continuous infusion is required to achieve a prolonged pharmacological response. The clinical studies conducted to define the pharmacokinetics of esmolol and its acid metabolite in humans have provided the basis for the subsequent dosage regimen employed in clinical trials. It was deduced from computer modeling that following a loading dose infusion of esmolol and a maintenance infusion, esmolol blood levels and beta blockade are at a steady state within 5 minutes (if a loading dosage is omitted, computer simulations suggest that approximately 45 minutes might be required to reach steady state blood levels). Using an appropriate loading dose, steady state blood levels of esmolol for dosages from 50-300 mcg/kg/min are readily obtained within 5 minutes. Blood levels of esmolol increased linearly over this dosage range. While steady state blood levels are maintained during infusion, they decrease rapidly after termination of the infusion. The elimination half life of esmolol after IV infusion is approximately 9 minutes. Hence, because of its short half life and rapid metabolism blood levels of esmolol can be rapidly altered by increasing or decreasing the infusion rate. Elimination kinetics of the drug have also been found to be independent of the dosage in the range 50-300 mcg/kg/min. Within 24 hours at the end of infusion, 73-88% of the dosage has been accounted for in the urine as the acid metabolite of esmolol. The kinetics of the acid metabolite have been found to be independent of the dose while its elimination half life is about 3.7 hours. The total body clearance is equivalent to the glomerular filtration rate. Methanol blood levels, monitored in patients receiving esmolol for up to 6 hours and 24 hours at 150 mcg/kg/min were usually within endogenous levels and always at least 2 orders of magnitude below those levels associated with methanol toxicity. Esmlol was shown to be 55% bound to human plasma protein while the acid metabolite was only 10% bound.

c. Pharmacodynamics

Seven studies (see Table A:8052-58, 43, 03, 15, 14, 13, 25) were primarly concerned with descriptive clinical pharmacology. The results are summarized below organized by major phenomena rather than by individual study.

1. Beta Blockade

Overview Summary

I) Request for Additional Data

It was decided that the effects of beta blockade could be better assessed if the data were plotted in semilog format. Therefore, re Studies 58, 43 and 03 the following graphs were requested.