CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020181

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OCT 17 1997

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **20-181**

SUBMISSION DATE: **July 24, 1997**

BRAND NAME: **LIPOSYN III**

GENERIC NAME: **30% Intravenous Fat Emulsion Pharmacy Bulk Package**

SPONSOR: **Abbott Laboratories**
Hospital Products Division
Abbott Park, IL

REVIEWER: **Carolyn D. Jones, Ph.D.**

TYPE OF SUBMISSION: **Response to Not Approvable Letter**

SYNOPSIS:

This submission dated July 24, 1997 contains an assay validation package for the methods used to quantify triglycerides, cholesterol and free fatty acids in plasma using a 30% intravenous fat emulsion pharmacy bulk package product.

BACKGROUND:

Intravenous fat emulsions were first introduced to the United States in 1975 with the approval of the soybean oil-based emulsion, Intralipid 10%. In 1981, Abbott followed with Liposyn 20% and in 1984, Abbott introduced an emulsion containing a 50:50 blend of safflower and soybean oils which increased the linoleic acid [redacted] This new emulsion was designated Liposyn II, and it was manufactured in both a 10% and 20% concentration. Liposyn III, a composition similar to Intralipid in that it is a soybean oil-based emulsion was approved in September 1994. It was approved in both the 10% and 20% concentrations.

Currently no 30% intravenous fat emulsions are in the marketplace. This product is designed to provide nutritional content equal to the 10% and 20% solutions but with less water. The proposed dosage is 0.1 g of fat per kg body weight. This emulsion is a source of calories for patients requiring parenteral nutrition, and is also indicated as a source of essential fatty acids to prevent or reverse biochemical changes associated with essential fatty acid deficiency (EFAD) and the clinical manifestations of the deficiency (e.g., scaliness of skin, growth retardation, poor wound healing and sparse hair growth).

DRUG FORMULATION:

Liposyn III 30% contains 30% soybean oil, 1.8% egg phosphatides and 2.5% glycerin in water

for injection. Sodium hydroxide has been added for pH adjustment, pH 8.4 (6.0 to 9.0). Liposyn III 30% has an osmolarity of 293 mOsmol/L and a specific gravity of 0.985. The total caloric value of Liposyn III 30% is 29 kcal/mL. Of this total, approximately 1.5 kcal/mL is supplied as linoleic acid.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) has reviewed the method validation section submitted in support of NDA 20-181 which was submitted to the Agency on July 24, 1997. The provided information is acceptable.

/S/

APPEARS THIS WAY
ON ORIGINAL

10/7/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Hae Young Ahn, Ph.D., Team leader 10/10/97

FT initialed by Hae Young Ahn, Ph.D., Team leader /S/ 10/10/97

cc: NDA 20-181, HFD-510 (Colman, McCort), HFD-340 (Vishwanathan), HFD-870 (Ahn, Jones, M.Chen), CDR(Murphy).

"CM"

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-181**
SUBMISSION DATE:	**November 7, 1996**
BRAND NAME:	**LIPOSYN III**
GENERIC NAME:	**30% Intravenous Fat Emulsion Pharmacy Bulk Package**
SPONSOR:	**Abbott Laboratories** **Hospital Products Division** **Abbott Park, IL**
REVIEWER:	**Carolyn D. Jones, Ph.D.**
TYPE OF SUBMISSION:	**Biometrics Report of Phase I Safety Clearance Study-Minor Amendment** **AMENDED REVIEW**

SYNOPSIS:

This submission dated November 7, 1996 contains a biometrics study report (Study No. 92010) for a Phase I Safety Clearance Study using a 30% intravenous fat emulsion pharmacy bulk package product. The objective of this uncontrolled, Phase I study was twofold: 1) to determine the safety of administration of a 30% intravenous fat emulsion and 2) to determine the rate of clearance of triglyceride and/or circulating cholesterol and free fatty acids from the blood of healthy volunteers after administration of 0.1 g of fat per kilogram body weight of Liposyn III 30%.

BACKGROUND:

Intravenous fat emulsions were first introduced to the United States in 1975 with the approval of the soybean oil-based emulsion, Intralipid 10%. In 1981 Abbott followed with Liposyn 20% and in 1984, Abbott introduced an emulsion containing a 50:50 blend of safflower and soybean oils which increased the linoleic acid This new emulsion was designated Liposyn II, and it was manufactured in both 10% and 20% concentrations. A composition similar to Intralipid was approved in September 1994 and was designated Liposyn III. It was approved in both the 10% and 20% concentrations.

Currently no 30% intravenous fat emulsions are in the marketplace. This product is designed to provide nutritional content equal to the 10% and 20% solutions but with less water. The proposed dosage is 0.1 g of fat per kg body weight. This emulsion is a source of calories for patients requiring parenteral nutrition, and is also indicated as a source of essential fatty acids to prevent or reverse biochemical changes associated with essential fatty acid deficiency (EFAD)

and the clinical manifestations of the deficiency (e.g., scaliness of skin, growth retardation, poor wound healing and sparse hair growth).

In response to the sponsor's waiver request for not needing in vivo bioavailability data that was reviewed by Daniel Gordin (10 April 1991), the waiver request was denied because of concerns that an increase in fat concentration could alter the elimination kinetics of the fat emulsion. It was suggested that the sponsor conduct a study comparing the elimination kinetics of the 30% Liposyn III to the 10% and 20% Liposyn III. However, this suggestion was not communicated to the sponsor in its entirety.

DRUG FORMULATION:

Liposyn III 30% contains 30% soybean oil, 1.8% egg phosphatides and 2.5% glycerin in water for injection. Sodium hydroxide has been added for pH adjustment, pH 8.4 (6.0 to 9.0). Liposyn III 30% has an osmolarity of 293 mOsmol/L and a specific gravity of 0.985. The total caloric value of Liposyn III 30% including fat, phospholipid and glycerol is 29 kcal/mL. Of this total, approximately 1.5 kcal/mL is supplied as linoleic acid.

ANALYTICAL METHODS:

No analytical method report or validation was provided for the analysis

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

In this submission the sponsor conducted a study with 12 healthy male volunteers (ranging in age from . years of age, mean age 32 years), who were administered 0.1 g of fat per kilogram body weight Liposyn III 30%. Of the 12 volunteers, only 10 completed the study. An intravenous infusion was administered over a range of 16 to 19 minutes. The time for administered triglycerides to be cleared from the blood was determined. This parameter was defined as the time at which the regression equation indicated that the triglyceride level had returned to baseline level. Clearance times of circulating cholesterol and free fatty acids from the blood were not calculated because no increases (the graphs were virtually flat) in lipid levels and free fatty acids were observed.

During administration of the infusion, the sponsor indicated all subjects received the identical food and fluid intake. However, the sponsor did not submit any information about the type of diet. The dietary intake was not controlled between the 60 minute and the 24-hour post-infusion time period. This lack of control of diet may explain the slight increases seen in triglyceride and cholesterol levels at the 24-hour time point.

An increase in triglyceride levels was observed at 10 minutes post-infusion with a return to normal range by 40 minutes. The mean half-life was 25.51 minutes, the mean clearance time was 3.22 hours and the mean triglyceride change from baseline was an increase of 37 mg/dL at the 60-minute post-infusion point (Figure 1).

Cholesterol levels, on the other hand, remained fairly constant during the 60 minute time period. The mean change from baseline for cholesterol levels was a decrease of 3 mg/dL at the 60 minute post-infusion time point. The mean cholesterol levels were within the normal range throughout the study (Figure 2).

Free fatty acid levels for the individual plots were relatively flat for all subjects, except one who had very high levels of free fatty acids compared to the other subjects. However, the levels did return to normal by 24 hours post-infusion. This subject was responsible for the high variability noted in the mean fatty acid graph (Figure 3). The mean change in free fatty acids was 0.337 mEq/L.

This study did show that triglycerides, but not free fatty acids and cholesterol, did change as a result of administration of the Liposyn III. However, the values were normal at the end of the 24-hour time period.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPEII) has reviewed the amendment that was submitted November 7, 1996 to NDA 20-181. Based upon this review, additional information is needed. Specifically, an acceptable assay validation is needed for the methods used to

The recommendation should be communicated to the sponsor as appropriate.

/S/

APPEARS THIS WAY
ON ORIGINAL

2/14/97
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Hae Young Ahn, Ph.D., Team leader 2/13/97

FT initialed by Hae Young Ahn, Ph.D., Team leader /S/ 2/14/97

cc: NDA 20-181, HFD-510 (Colman, McCort), HFD-340 (Vishwanathan), HFD-870 (Ahn, Jones, M.Chen), HFD-850(Millison).

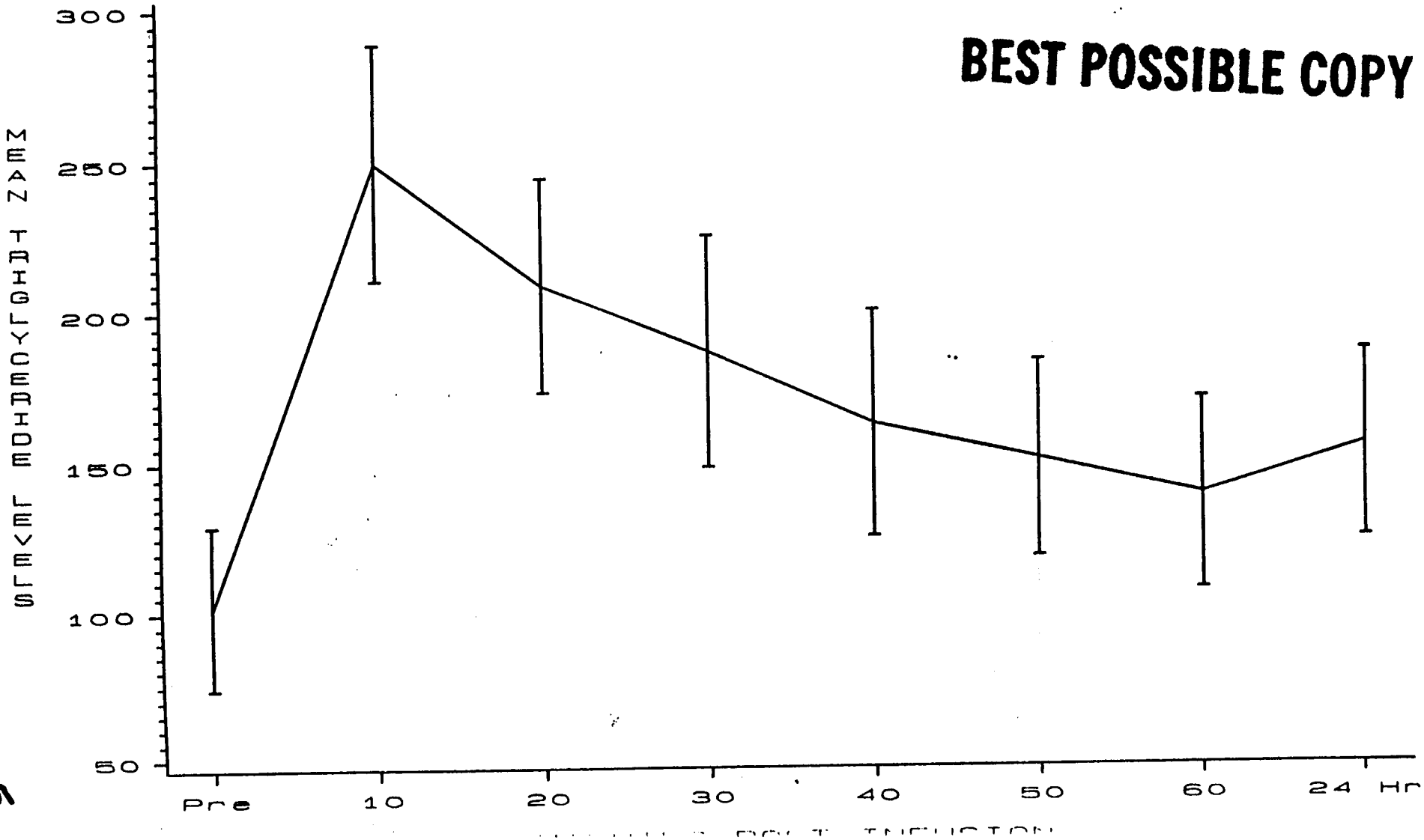
APPEARS THIS WAY
ON ORIGINAL

Abbc Study 92010

Liposyn III 30% Clearance Study

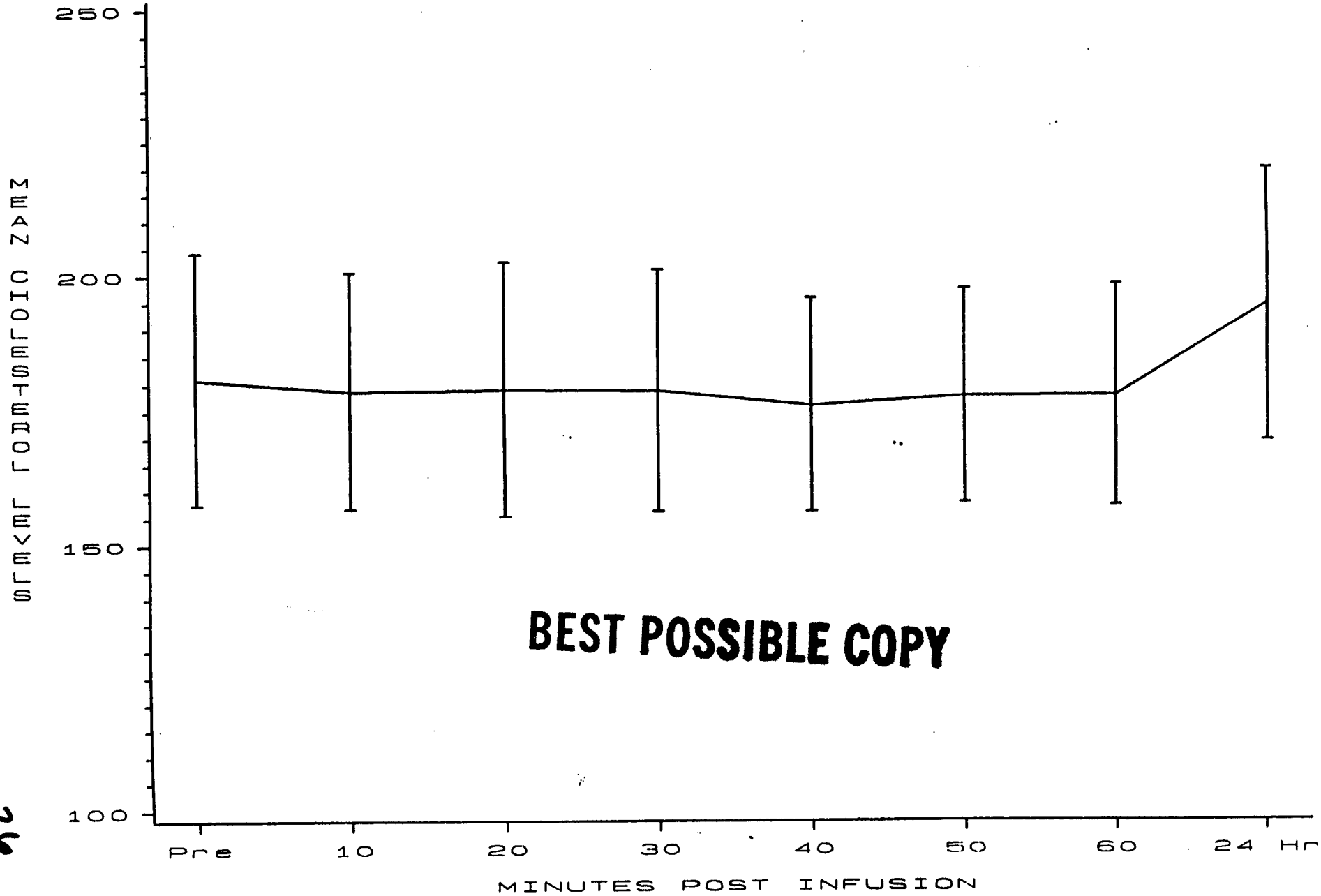
Triglyceride Levels (mg/dL) Across Time

Figure 1



Cholesterol Levels (mg/dL) Across Time

Figure 2

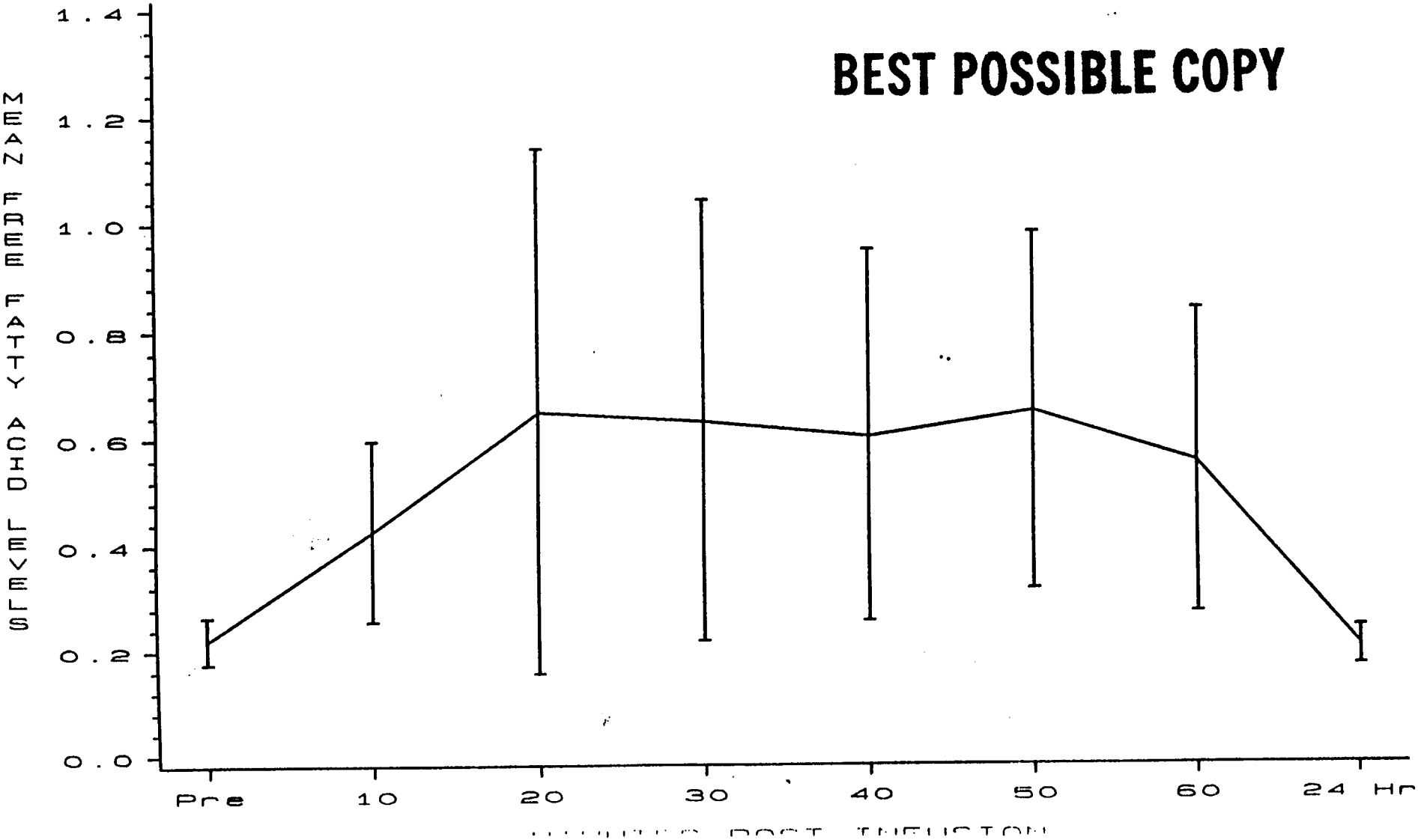


Abbc Study 92010

Liposyn III 30% Clearance Study

Free Fatty Acid Levels (meq/l) Across Time

Figure 3



CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: **20-181**

SUBMISSION DATE: **November 7, 1996**

BRAND NAME: **LIPOSYN III**

GENERIC NAME: **30% Intravenous Fat Emulsion Pharmacy Bulk Package**

SPONSOR: **Abbott Laboratories**
Hospital Products Division
Abbott Park, IL

REVIEWER: **Carolyn D. Jones, Ph.D.**

TYPE OF SUBMISSION: **Biometrics Report of Phase I Safety Clearance Study**

SYNOPSIS:

This submission dated November 7, 1996 contains a biometrics study report (Study No. 92010) for a Phase I Safety Clearance Study using a 30% intravenous fat emulsion pharmacy bulk package product.

RECOMMENDATION:

The biometrics study report submitted on November 7, 1996 to NDA 20-181 will not be reviewed by the Office of Clinical Pharmacology and Biopharmaceutics (OCPB)/Division of Pharmaceutical Evaluation II (DPE II) because the submission is for pharmacy bulk package products and it is a safety clearance study.

/S/

APPEARS THIS WAY
ON ORIGINAL

12/11/96
Carolyn D. Jones, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Hae Young Ahn, Ph.D., Team leader 12/11/96

FT initialed by hae Young Ahn, Ph.D., Team leader /S/ 12/11/96

cc: NDA 20-181, HFD-510 (Colman, McCort), HFD-870 (Ahn, Jones, M.Chen), HFD-870(Bott, Chron, Drug, Reviewer)

WAIVER Denied by mistake

MAY 15 1991

LIPOSYN III 30%
NDA 20-181
Reviewer: M. Daniel Gordin, Ph.D.

Abbott
Abbott Park, IL
Submission Date
April 10, 1991

REVIEW OF A WAIVER REQUEST

BACKGROUND:

In this submission, the firm has submitted a request for a waiver of in vivo bioavailability testing for this product. According to 21 CFR 320.22 (b) (1), the FDA shall waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if i) it is a solution intended solely for intravenous administration, and ii) the product contains an active ingredient or therapeutic moiety in the same solvent and concentration that is the subject of an approved NDA application.

The sponsor states "The subject drug is identical in qualitative composition to that of our currently approved Liposyn III 10% and 20% products included in NDAs 18-969 and 18-970 but differs in the fat concentration and its intended use only as a Pharmacy Bulk Package."

RECOMMENDATION:

This waiver request does not meet the technical requirement as specified under 21 CFR 320.22 (b)(1)(ii) since its fat concentration is not the same concentration as the approved NDA (i.e. 10% and 20%)

You should address the feasibility of conducting such a study in which the elimination kinetics of the 30% Liposyn is compared to the 10% and 20% Liposyn.

Please convey the Recommendation to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

/S/
M. Daniel Gordin, Ph.D.
Pharmacokinetics Evaluation Branch

RD Initialed/FT Initialed by John P. Hunt /S/ 5/14/91

cc: Orig, HFD-160, HFD-426 (Gordin), Drug, Chron, and HFD-19 (FOI).

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JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

Vol. 11, No. 1
Printed in U.S.A.

Elimination Kinetics of Lipofundin MCT: Bolus Injection and Infusion Compared*

W. LEONHARDT AND U. JULIUS

From the Department of Internal Medicine, Medical Academy "Carl Gustav Carus," Dresden, GDR

ABSTRACT. Fifteen healthy young probands (nine males, six females) underwent an intravenous fat tolerance test (IVFTT) and, on the following day, a fat infusion lasting 6 hr. The emulsion tested was Lipofundin MCT 10%. One half of its triglyceride mass contains medium chain fatty acids. The IVFTT was started by injection of 0.1 g lipid per kg body weight into the fasting proband. Lipid elimination was estimated by measurement of light-scattering intensity of serum samples collected during a 60-min period. Individual fraction elimination rate constants covered a considerable range (K_2 = 5.54 ± 3.45%/min). The infusion test was performed at a rate of 0.1 g lipid per kg body weight and hr and lasted 6 hr. Serum triglyceride concentrations were determined enzymatically. They increased from 0.941 ± 0.285 mmol/liter at the fasting state to a plateau level of 1.753 ± 0.306 mmol/liter during infusion, and returned to initial levels 1 to 2 hr after the infusion was terminated. Individual triglyceride increments during infusion were significantly correlated with half-life periods of lipid elimination during IVFTT ($r = 0.792$, $p < 0.001$). This relationship was derived using a model of the stationary state during infusion. We conclude that elimination kinetics of exogenous fat given either as bolus or infusion are ruled by the same fractional elimination rate constant K_2. The IVFTT provides an estimate of the stationary triglyceride increment during a lipid infusion lasting several hr. (*Journal of Parenteral and Enteral Nutrition* 11:57–59, 1987)

In using lipid emulsions in parenteral nutrition, the general dosage regimen recommendation for adults is 0.1 g of lipid per kg body weight an hr.[1-3] For patients suffering from hypertriglyceridemia, this rate may be too high in individual cases. In most of them, the triglyceride (TG) elimination capacity is limited or significantly diminished,[4-8] and it is possible that a steep rise in TG concentrations during infusion induces adverse effects. The intravenous fat tolerance test (IVFTT)[4] provides a simple method to check TG elimination capacity, although it does not yield information as to which organ systems are involved in fat uptake, or as to the metabolic steps following elimination. There exists a negative correlation between the fractional elimination rate constant K_2 and the fasting level of TG.[4,6,8,9]

In a recent paper, it was shown that elimination parameters for a single bolus dose of lipid emulsion cannot be used to predict the manner in which a continuously infused dose will be eliminated.[10] No literature data are available that compare intraindividually the elimination capacity for exogenous fat injected as a bolus with the lipemia during infusion of the same fat. We performed such a study in healthy young probands. Divergent lipid elimination capacities can be expected, even in such a group with normolipemia.[6,11] The lipid emulsion tested was a medium chain triglyceride (MCT)-containing preparation. One half of its triglyceride mass contains medium chain fatty acids which are readily eliminated and metabolized in parenteral nutrition.[12]

Received for publication, December 3, 1985.
Accepted for publication, May 13, 1986.
Reprint requests: Dr. Wolfgang Leonhardt, Department of Internal Medicine, Medical Academy Carl Gustav Carus, Postanschrift: [illegible], Dresden, German Democratic Republic.
* Dedicated to Hans Haller on the occasion of his 65th birthday.

MATERIALS AND METHODS

The baseline data of the 15 persons tested are given in Table I. All laboratory parameters were in the normal range; acute diseases were absent. None of the young people smoked; the females did not receive any oral contraceptives. Probands were fully informed on aims and conditions of the tests and gave their written consent.

The tested lipid emulsion was Lipofundin MCT 10%: 1000 ml of the preparation contain 50 g of soybean oil, 50 g of medium chain triglycerides, 12 g of egg yolk lecithin, and 25 g of glycerol.[12] The IVFTT was performed in the morning, after the probands had been fasting for at least 12 hr.[6,8] The emulsion (1 ml/kg body weight) was injected into the proband in a supine position within 1 min. Blood samples were taken from the vein of the contralateral arm at 0, 5, 10 . . . 35, 40, and 60 min. Serum was diluted 1:16 with saline, and light-scattering intensity was measured on a Zeiss nephelometer at 650 nm. The value at $t = 0$ min was subtracted from all readings. The differences decrease with sampling time following an exponential function. This was evaluated by regression analysis in a semilogarithmic system. The regression coefficient multiplied by 100 is the fractional elimination rate constant K_2 (%/min). The variation coefficient of K_2 is a measure of precision of a single test. In this study, we observed 9.2% on average. The half-life period was estimated according to $t_{½} = 69.3/K_2$.

On the following morning, Lipofundin MCT 10% was infused into the fasting probands at a rate of 1 ml/kg body weight an hr over a period of 6 hr. Blood samples were taken at 0, 1, 2, 3, 4, 5, and 6 hr during infusion, and 0.5, 1, 1.5, and 2 hr after infusion. Serum triglycerides were assessed by chemical saponification and enzymatic determination of glycerol with test kits (Boehringer-

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JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

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Elimination and Metabolism of a Fat Emulsion Containing Medium Chain Triglycerides (Lipofundin MCT 10%)

ULRICH JULIUS, M.D. AND WOLFGANG LEONHARDT, PH.D.

From the Clinic of Internal Medicine, Medical Academy "Carl Gustav Carus," Dresden, GDR

ABSTRACT. Medium chain triglycerides (MCT) are supposed to be advantageous on account of rapid energy supply in parental nutrition. However, data on the elimination rate of MCT-containing emulsions during an intravenous fat-tolerance test (IVFTT) are scarce. We performed this test (0.1 g lipid/kg body weight) in 18 young healthy volunteers (nine females and nine males) using Lipofundin MCT 10% (50% MCT; egg phospholipids as emulsifier). Our results indicate that both elimination and metabolization of the emulsion are fast: a prompt decrease of light-scattering index and of triglyceride concentrations in serum, an immediate appearance of post-load fatty acids and of β-hydroxybutyrate were observed. This was in good agreement with the findings obtained during 6-hr infusions in the same probands.

Fractional elimination rates k_2 obtained from light-scattering indices are 7.29 ± 2.73%/min in males and 11.59 ± 3.38%/min in females, indicating a higher removal capacity in women. In the same subjects, the corresponding k_2 values for Lipofundin S 10% (containing only long chain triglycerides) were higher, reflecting an elimination rate that is faster due to the use of soya bean phospholipids as emulsifier. In comparison, k_2 values based on the course of the triglyceride concentrations are generally lower. (*Journal of Parenteral and Enteral Nutrition* 12:116–120, 1988)

In order to supply energy to a patient by intravenous infusion of a fat emulsion, the exogenous triglycerides (TG) must be removed from the bloodstream and metabolized.[1] With regard to intracellular metabolization, medium-chain triglycerides (MCT) have been reported to be advantageous.[2–6]

TG concentrations during infusions of MCT-containing fat emulsions have been found to be lower than during infusions that contain long chain triglycerides (LCT) only.[5,7,8] However, the emulsifier of the first MCT-containing emulsions consisted of soya bean phosphatides,[3,5,7] the latter have recently been replaced by egg yolk phospholipids. For LCT emulsions, it is known that egg yolk phospholipids give rise to a slower rate of elimination.[9,10] Therefore, we were interested in testing the effect of this type of emulsifier on the MCT-containing emulsion.

In addition, our study aimed at answering several other questions. Are the elimination rates identical when their calculation is based on measurements of light-scattering index (LSI) or of TG concentrations? Is it possible to reproduce interindividual differences in the fat elimination capacity, for instance, between males and females, with different fat emulsions? Does there exist a parallelity between elimination and metabolization data that have been obtained during an intravenous fat tolerance test (IVFTT) and during an infusion?

We approached these problems in young healthy probands by performing both IVFTT and infusions with Lipofundin MCT 10% (50% of its fat as MCT, egg yolk phospholipids) and by studying the elimination kinetics of Lipofundin S 10% (containing exclusively LCT, soya bean phospholipids) during an IVFTT in the same probands.

Received for publication, July 22, 1986.
Accepted for publication, January 26, 1987.
Reprint requests: OA Dr. sc. med. U. Julius, Medizinische Akademie "Carl Gustav Carus," Klinik für Innere Medizin, Fetscherstr. 74, Dresden, 8019, GDR

MATERIAL AND METHODS

We tested 18 young volunteers (medical students), nine females and nine males, aged from 22 to 27 yr, who were nonobese (ideal body weight index from 92 to 108%) and had normal glucose tolerance. The lipid baseline data are given in Table I and are in the normal range.

Clinically, and with regard to other laboratory parameters (erythrocyte sedimentation rate, blood count, ALAT, creatinine, Na^+, K^+), the existence of acute diseases could be excluded. All the young people were nonsmokers, the females did not take any oral contraceptives. The students were fully informed about the testing procedure and the aims of the study, and gave their written consent.

Two lipid emulsions were used in the same probands: Lipofundin MCT 10%, which is composed of MCT and LCT, and Lipofundin S 10%, containing only LCT (see Table II).

The dominating component of LCT (soya bean oil) is linoleic acid, whereas MCT represent mainly octanoic and capric acids.[11] The emulsions differed also with respect to the emulsifier and the content of xylit and glycerol, respectively.

Lipofundin MCT 10%

IVFTT. After an overnight fast, 0.1 g fat/kg body weight was injected as a bolus to the recumbent proband within 1 min. Blood samples were taken from the vein of the contralateral arm at 0, 5, 10, 15, 20, 25, 30, 35, 40, and 60 min.

Infusion. On the next day, in the same fasting students an infusion of this lipid emulsion was started at 8 am