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INTRAVENOUS INFUSION OF FAT EMULSION. EXPERIMENTAL AND CLINICAL STUDIES ON INTRAFAT

BY

Nobuyoshi KIMURA, Eiichi YAMADA, Kenji TERADA, Kazuto MURAKAMI and Masuo IIZUKA*1

ABSTRACT

Experimental and clinical studies on Intrafat*2 (DI-22), a fat emulsion for intravenous infusion which was recently developed in Japan, were conducted. Intrafat consists of a 10% solution of soya bean oil and as an emulsifier egg yolk phospholipid which is added to stabilize the emulsion, and to make it isotonic a 2.5% glycerol is added.

During the past 18 years we studied the many aspects concerning the use of emulsified soya bean oil for tube feeding to be used for the nutritional management of patients undergoing operations.

Recently we in Japan have been able to develop such a fat emulsion to be administered intravenously, whereby an equal amount of fat as in tube feeding can be introduced.

The side effects of Intrafat were very mild and no sign of overloading syndrome was observed. Intrafat is not only safe for clinical use but valuable for studies of metabolic changes to be made in the future.

INTRODUCTION

In recent years much progress has been made in the nutritional management of surgical patients. One of the big steps forward has been the introduction of an adequate amount of fat to be given safely but this has presented many problems. During the past ten years we reported on the many aspects concerning the use of emulsified soya bean oil for tube feeding to be used for the nutritional management of patients undergoing operations. Very recently we in Japan have been able to develop an emulsified fat solution to be administered intravenously whereby an equal amount of fat as in tube feeding can be introduced.

This is the first of the many reports to follow on our experimental and clinical investigations concerning our intravenous emulsified fat solution.

*1 木村信良，山田栄一，寺田健治，村上一登，飯塚益生: Second Department of Surgery (Chief: Prof. E. HAMAGUCHI), School of Medicine, Tokyo Medical and Dental University (Tokyo Ika Shika Daigaku).

*2 The fat emulsion, Intrafat was manufactured and supplied by Daigo Nutritive Chemicals, Ltd.

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INGREDIENTS AND CHARACTERISTICS OF INTRAVENOUS FAT EMULSION (INTRAFAT)

1) Ingredients

Intrafat, an intravenous fat solution developed in Japan consists of a 10% solution of soya bean oil and as an emulsifier egg yolk phospholipid, which is added to stabilize the emulsion, and to make this isotonic a 2.5% glycerol is added (Table 1).

The gaschromatographical analysis of the fatty acid showed it to consist in the order of linoleic acid, oleic acid, plamitic acid, etc., and the unsaturated fatty acid content is about 75.6% (Fig. 1, Table 2).

2) Electron microscopic findings

Intrafat was diluted to about 1:1,000 with distilled water and a drop of this diluted emulsion was placed on copper grids covered with a thin collodion membrane. The drop was evaporated to dryness at room temperature, and when the size and shape of the fat particles in Intrafat was observed under an electron microscope magnified 1:5,000, the diameter was

Table 1. Composition of the fat emulsion

Soy bean oil	10.0 g
Phospholipid	1.2 g
Glycerol	2.5 g
Aq. dest.	ad. 100 ml

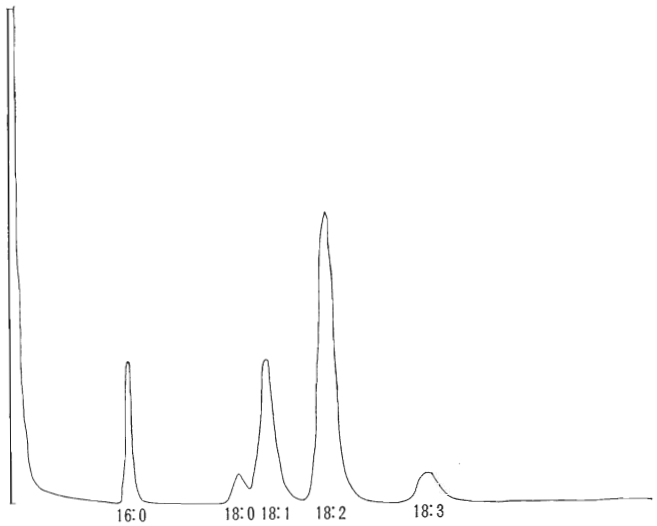

Fig. 1. The gaschromatographic analysis of fat emulsion.

Table 2. Fatty acid constituents of fat emulsion

		(%)
Myristic	acid (C14:0)	—
Palmitic	acid (C16:0)	12.41
Palmitoleic	acid (C16:1)	—
Stearic	acid (C18:0)	4.36
Oleic	acid (C18:1)	23.92
Linoleic	acid (C18:2)	51.63
Linolenic	acid (C18:3)	7.68

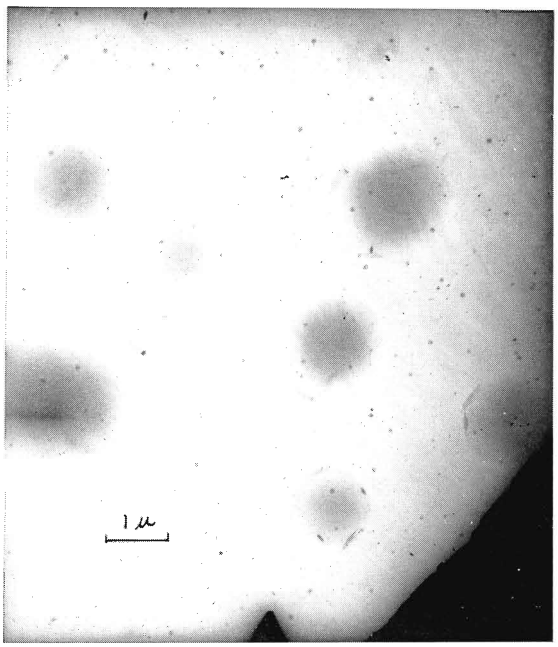

Fig. 2. Electron microscopic findings.

between 0.2 μ to 1.2 μ (average 0.8 μ to 1.0 μ) as shown in Fig. 2 and the particles were almost uniformly round in shape. The center of the fat particle had a concentrated core around which there was a less concentrated layer. This concentrated layer composed possibly of a phospholipid plays an important role in stabilizing the emulsion[1].

3) Combination tests with other solutions for intravenous

Clinically when Intrafat is to be administered intravenously it would be combined with the other intravenous solutions or it is possible that it would still remain in the blood stream when other intravenous preparations are introduced. For this reason we were faced with the important problem

Table 3. Combination test with other solution

Mixture Ratio / Solution	Solution : Intrafat 1 : 1	Solution : Intrafat : Serum 1 : 1 : 1
4% Glucose	−	−
10% Glucose	−	−
50% Glucose	−	−
5% Xylitol	−	−
10% Xylitol	−	−
50% Xylitol	−	−
Ringer's Solution	+	−
Physiol. Salt Solution	+	−
Ringer's Solution with Sodium lactate	+	−
Physiol. Salt Solution with Sodium lactate	+	−
M/6 Ammonium chloride	+	−
Mixed Amino Acids Solution	−	−
P V P	##	##
Modified Fluid Gelatin	##	##
Low Molecular Dextran	##	##

\+ Swelling of the fat particle and some aggregation of the particle
Remarkable aggregation

Table 4. Mixture test with modified fluid gelatin, low molecular dextran and polyvinylpyrrolidone

Plasma / Plasma expander	0°	1°	3°	6°	12°	48°	72°	96°
Modified fluid Gelatin	##	##	##	##	+	+	+	+
Low mol. Dextran (Mw 40,000)	##	##	##	##	+	+	+	−
P V P	##	+	+	+	+	+	−	−

\+～## : degree of aggregation

of whether or not changes occur in the characteristics of the emulsion when mixed either before or after entering the blood stream.

Tests *in vitro* at a temperature maintained at 38°C were performed, using a) Intrafat and other intravenous solutions combined in equal proportions, and b) Intrafat, other solutions and human serum mixed in a proportion of 1:1:1. The results are shown in Table 3. When the electrolyte solutions and Intrafat were combined swelling of the fat particles (over

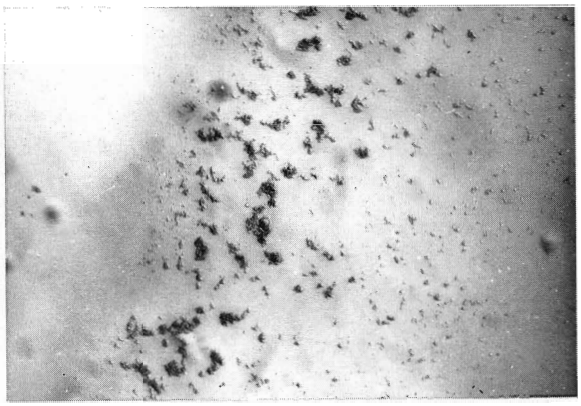

Fig. 3. Microscopic finding of the mixture test with modified fluid gelatin.

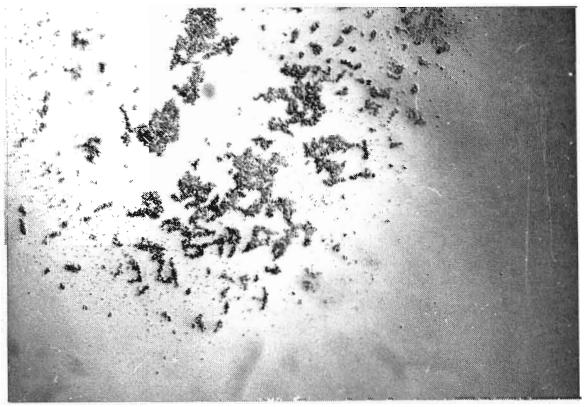

Fig. 4. Microscopic finding of the mixture test with low molecular dextran.

2 μ in diameter) and some aggregation of the particles were noted. In other words, with a Y tube Intrafat can be introduced at the same time as glucose or other amino acid solutions but the combination of Intrafat and electrolyte solutions was found to have its problems but if the human serum were combined to this combination is equal proportions (1:1:1) no aggregation was noted. For this reason it is believed that even if the electrolytes and Intrafat are administered at the same time aggregation does not occur in the blood stream nor is there swelling of the fat particles.

On the other hand, combination tests were performed with plasma expanders such as modified fluid gelatin, Dextran and PVP, and it was observed microscopically that aggregation occurred when the emulsion came in contact with the blood or plasma of a person given plasma ex-

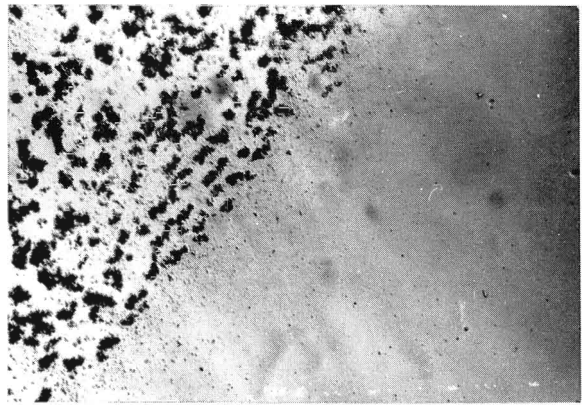

Fig. 5. Microscopic finding of the mixture test with polyvinylpyrrolidone.

pander, even when nine hours had passed after the injection, at which time the plasma expander should have almost disappeared from the blood stream (Table 4, Figs. 3, 4 and 5). This fact makes us believe that one should not use this fat emulsion in combination with plasma expanders.

Experimental Studies (Dogs)

Wretlind[2] has published many articles on Intralipid which has the same composition as Intrafat except for a few minor differences. We performed studies on dogs to compare Intrafat with Intralipid and the results are shown in Figs. 6 and 7. There was a difference in the quantity of fat

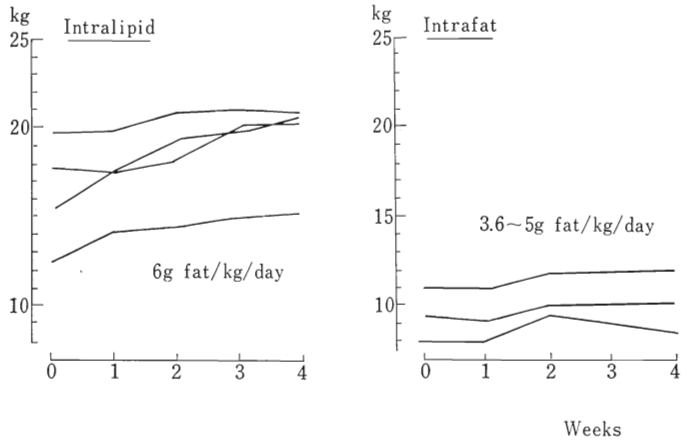

Fig. 6. The changes of body weight in dogs on intravenous infusion of fat emulsion.

administered between Intrafat, which was 3.6 to 5.0 grams of fat per kilogram of body weight per day and Intralipid which was given in a quantity of 6.0 grams fat/kg/day. These amounts were administered for 4 consecutive weeks whereupon no decrease of body weight was noted with Intrafat while a slight increase was noted with Intralipid. The same curve was observed in the hematocrit and hemoglobin with Intralipid and Intrafat, and even with prolonged administration of Intrafat no decrease in either, the hemoglobin hematcrit was observed which differs from the reports concerning other emulsions such as Lipomul, Lipofundin and Lipophysan, etc., which caused severe anemia[3].

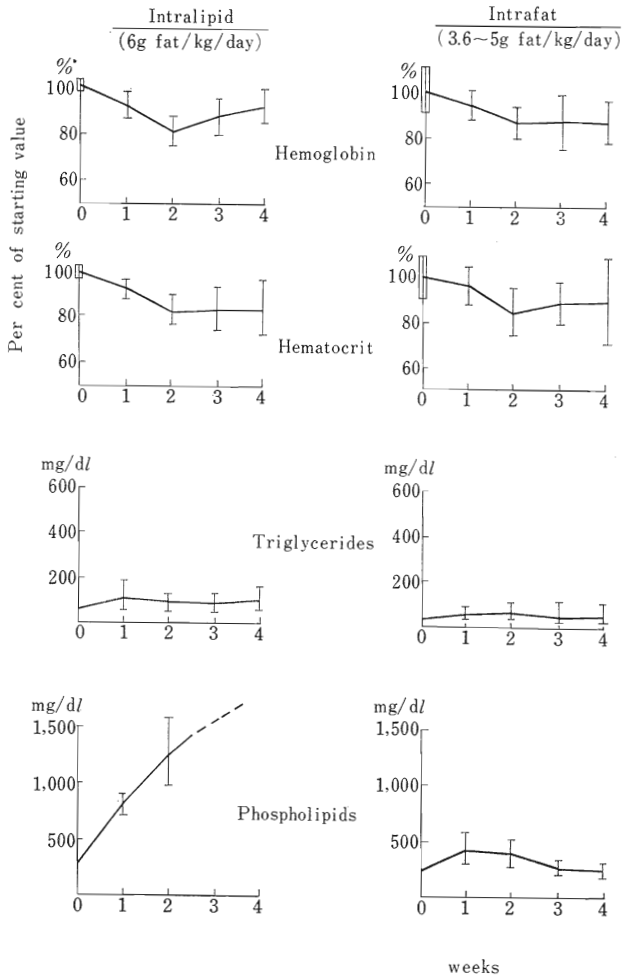

Fig. 7. The effects of intravenous fat infusion on the hemoglobin, hematcrit and plasma lipids in the dog.

The plasma lipid fluctuation of Intrafat and Intralipid showed that with the prolonged use, plasma triglyceride increased but no tendency of accumulation was noted. On the other hand, plasma phospholipid did not increase with Intrafat but with Intralipid an increase was noted in one

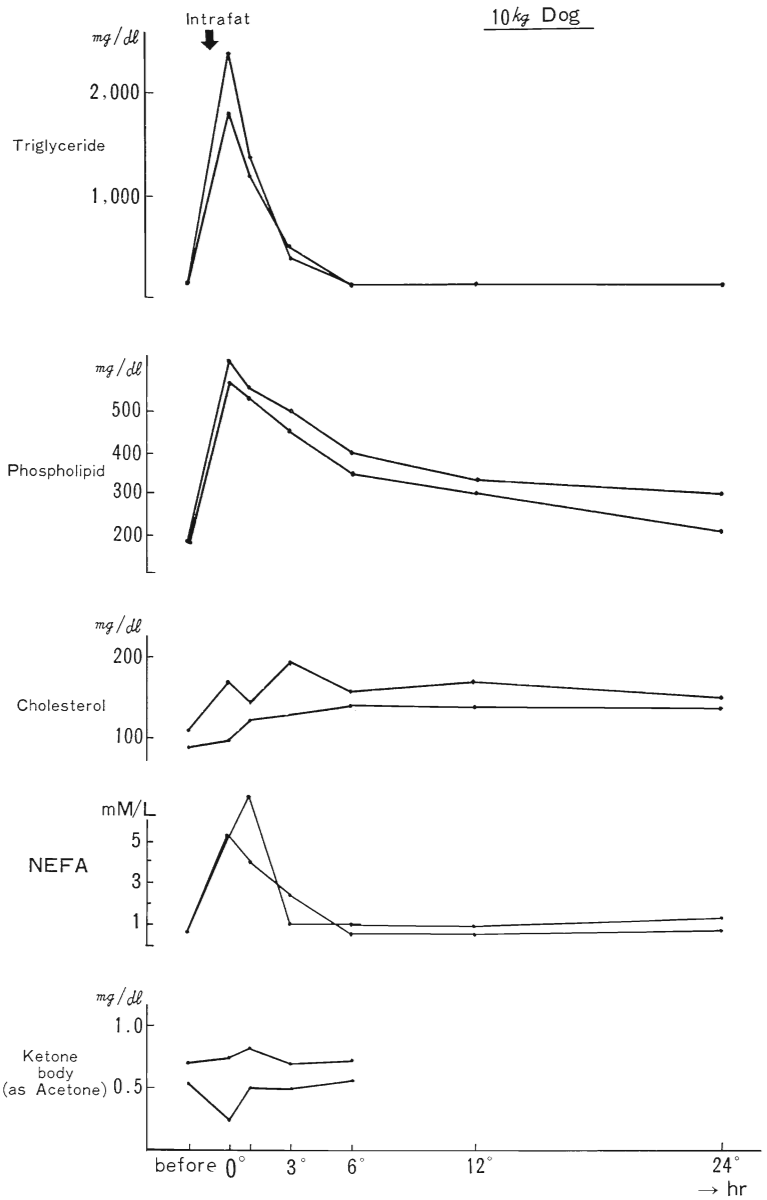

Fig. 8. The fluctuation of keton bodies and plasma lipids after Intrafat (2 g/kg) injection.

week. This difference according to Wretlind is related to the amount administered per kilogram of body weight.

Wretlind reports that when Intralipid is administered in increased quantities, up to 9.0 gram of fat per kilogram of body weight for a long period of time, vomiting of a mild degree was noted and the blood triglyceride increased in some cases[2]. In quantities less than 6.0 grams fat/kg/day both Intrafat and Intralipid showed no side effects and could be used for prolonged periods of time. Fig. 8 shows the plasma lipid fluctuation with time when Intrafat was administered in quantities of 2.0 grams of fat per kilogram per day. It was made clear that in adults the level of triglyceride, phospholipid and free fatty acids returned to their pre-infused level within 6 to 12 hours when Intrafat was given in doses of 2.0 grams of fat per kilogram per day and no changes were noted in the keton bodies.

In view of the non-toxic effect and biochemical findings of Intrafat these results led us to conduct clinical investigations.

Clinical Investigations and Results

1) Subjects

Intrafat was administered mostly for pre- and post-operative nutrition and to terminal cases of cancer where an adequate amount of food could not be taken orally. The subjects were patients in the Second Surgical Department of Tokyo Medical and Dental University.

The age range was between 9 years to 78 years as shown in Table 5.

The total amount of Intrafat administered to each patient was between 200 ml to 1,400 ml (Table 6) and the daily amount for each patient was 500 ml of a 10% solution of Intrafat.

The speed of the injection was regulated so that it required over 3 hours to introduce the 500 ml. The method of injection was regulated so that the glucose and amino acid solutions were introduced first and only when the amount reached half of the daily requirement, was Intrafat added to the infusion using a Y tube.

As shown in Table 7 the majority of the patients given Intrafat were cases with gastric diseases and the operative methods used are shown in Table 8 for those cases given Intrafat postoperatively.

2) Clinical investigations

a) Side effects during Intrafat infusion (Table 9)

One hundred and eight subjects, a total of 298 injections, were infused with Intrafat.

A study on the side effects showed that there were no drastic side

Table 5. Sex and age of subjects

Age \ Sex	Male No. of Cases	Female No. of Cases
yrs 1～ 9	0	1
10～19	3	
20～29	7	4
30～39	12	4
40～49	10	3
50～59	11	7
60～69	15	6
70～	3	1
Total	61	26

Table 6. Dosage per case

Intrafat (*ml*)	No. of Cases
100	
200	2
300	4
400	3
500	32
1,000	2
1,500	3
2,000	3
2,500	29
3,000	4
3,500	1
4,000	1
4,500	
5,000	1
5,500	
6,000	1
14,000	1
Total	87

effects as noted with Fatgen although there was one case of nausea, one case of shivering and 3 cases of thrombophlebitis. The reactions were mild and very infrequent and no side effect was so severe that the injection had to terminated. Thrombophlebitis was noted when Interfat had been refrigerated and not been brought back to room temperature, and when warm compresses were applied proximally one was able to continue the injection.

b) Biochemical changes in the blood of postoperative patients given Intrafat (500 ml/day) infusions for 5 days

In order to administer an ideal nutrition to postgastrectomy patients Intrafat was given in combination with 500 ml of a 10% amino acid solution, 500 ml of Ringer's solution, and a 10% xylitol solution, and the pre- and post-operative biochemical data were compared with those of the controls not given Intrafat. The results of the hematcrit, hemoglobin, plasma protein, A/G ratio, blood sugar, liver function, serum urea nitrogen and thrombotest, etc. are shown in Figs. 9 and 10.

It was noted that Intrafat given for 5 consecutive postoperative days produced neither anemia nor hypoproteinemia. As compared to the controls no significant difference was noted in the liver function such as GOT, GPT and TTT levels. It was interesting to note that the thrombotest of the

Table 7. Kinds of diseases given fat emulsion

Gastric ulder	25
Gastroduodenalu ulcer	2
Duodenal ulcer	8
Postoperative stomal ulcer	1
Gastric polyp	2
Diverticulum of stomach	1
Gastric cancer	29
Pyrolic stenosis	1
Carcinoma of esophagus	1
Diaphragmatic hernia	1
Cholelithiasis	7
Biliary-duodenal fistula	1
Hepatic cancer	1
Crohn's disease	1
Peritonitis carcinomatosa	1
Pleuritis carcinomatosa	1
Carcinoma of thyroid	1
Tumor of Brain	1
Seminoma (Metastasis of lung)	1
Carcinoma of breast	1
	87 cases

Table 8. Kinds of operation of cases given fat emulsion

Operation	No. of cases
Gastrectomy B I	22
B II	30
Total gastrectomy+Splenectomy	6
Total gastrectomy+Splenectomy+partial resection of Pancreas	1
Resection of lower esophagus and Cardia	1
Gastroenterostomy	3
Cholecystomy	5
Cholecystectomy and Choledochus-drainage	2
Exploratory laparotomy	3
right side hemicolectomy	1
Herniorrhaphy	1
Total	75

Intrafat group did not show a tendency of increase in coagulaiton time.

When 500 ml per day of Intrafat were given for 5 days the lipid fluctuation was as shown in Fig. 11. In the group given Intrafat there was a tendency of increase in total triglyceride as compared to the control group

Table 9. Cases of side effects in 108 cases

Acute side effect		Late side effects or Overloading syndrome	
Cyanosis	0	Anemia	0
Dyspnea	0	Hyperlipemia	0
Chill	0	Gastro-intestinal bleeding	0
Haedache	0	Liver-damage	0
Anxiety of the breast	0	Pigment deposition	0
Pains in back	0	Prolong coagulation time	0
Pains in chest	0	Hemorrhagic diathesis	0
Nausea	1		
Vomiting	0		
Peculiar order	3		
Phlebitis	1		

but both groups showed a normal phospholipid level, and no tendency of accumulation was noted in the triglycerides and phospholipids in the Intrafat group.

c) Influence of Intrafat with long term usage

The number of cases administered Intrafat for over 10–15 days was small in number.

A comparative study was made on 1) cases where only glucose and amino acids were given parenterally, 2) cases where Intrafat, 500 ml/day, was administered for 5 days, 3) cases where Intrafat, 500 ml/day, was administered for over 10–15 days. The results showed that hemoglobin, hematocrit, serum protein and A/G ratio had a tendency to slightly decrease in those cases given Intrafat for a long period of time. This is believed to be influenced more by the original disease than by the fat emulsion. GOT, GPT, TTT, ZTT and alkaline phosphatase were studied as liver function tests but no significant difference was noted between the groups. It may be concluded that Intrafat has no untoward influence on the liver function. Also no difference was noted in the urea nitrogen, serum sodium and serum potassium level fluctuations.

Discussion

Long years of research for a complete intravenous solution containing complete nutrition, including the amino acids, carbohydrates and fat, has been made but an adequate amount of fat has always led to side effects. Therefore the real objective was not obtained.

The study on fat to be given parenterally started about 100 years ago

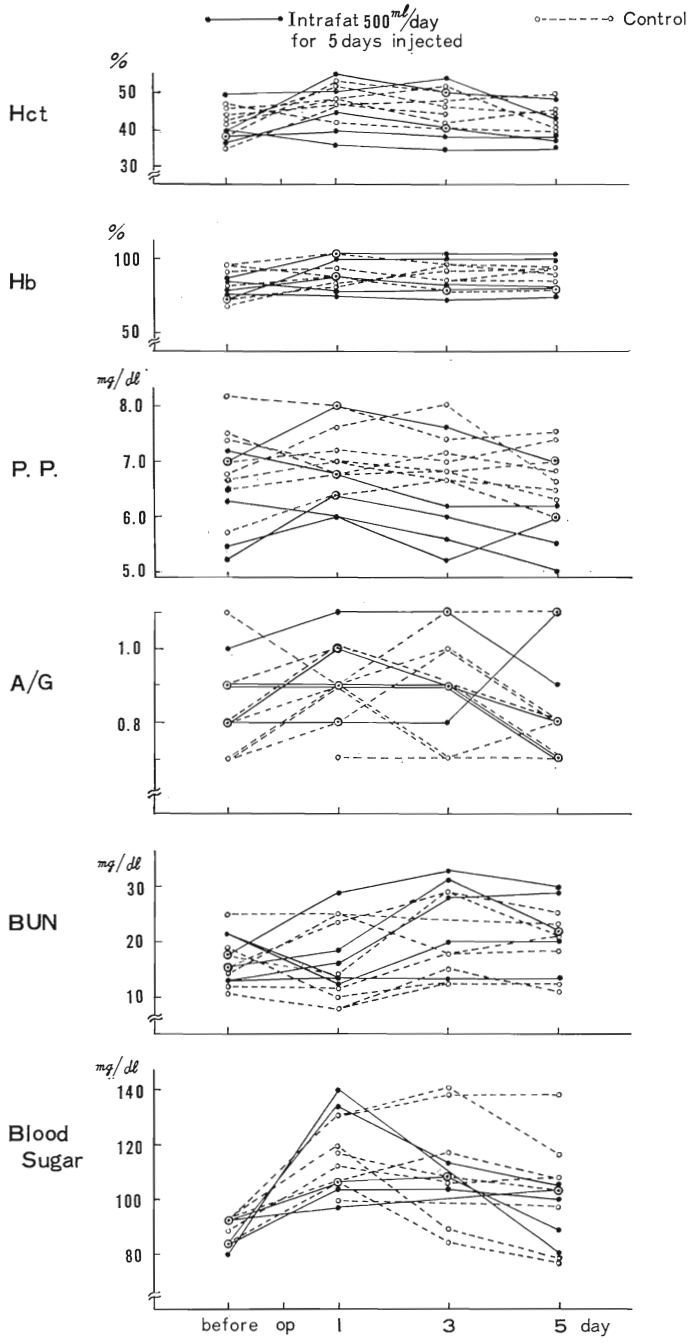

Fig. 9. The effects of intravenous fat infusions on hematcrit hemoglobin, plasma protein, A/G ratio, BUN and blood sugar level.

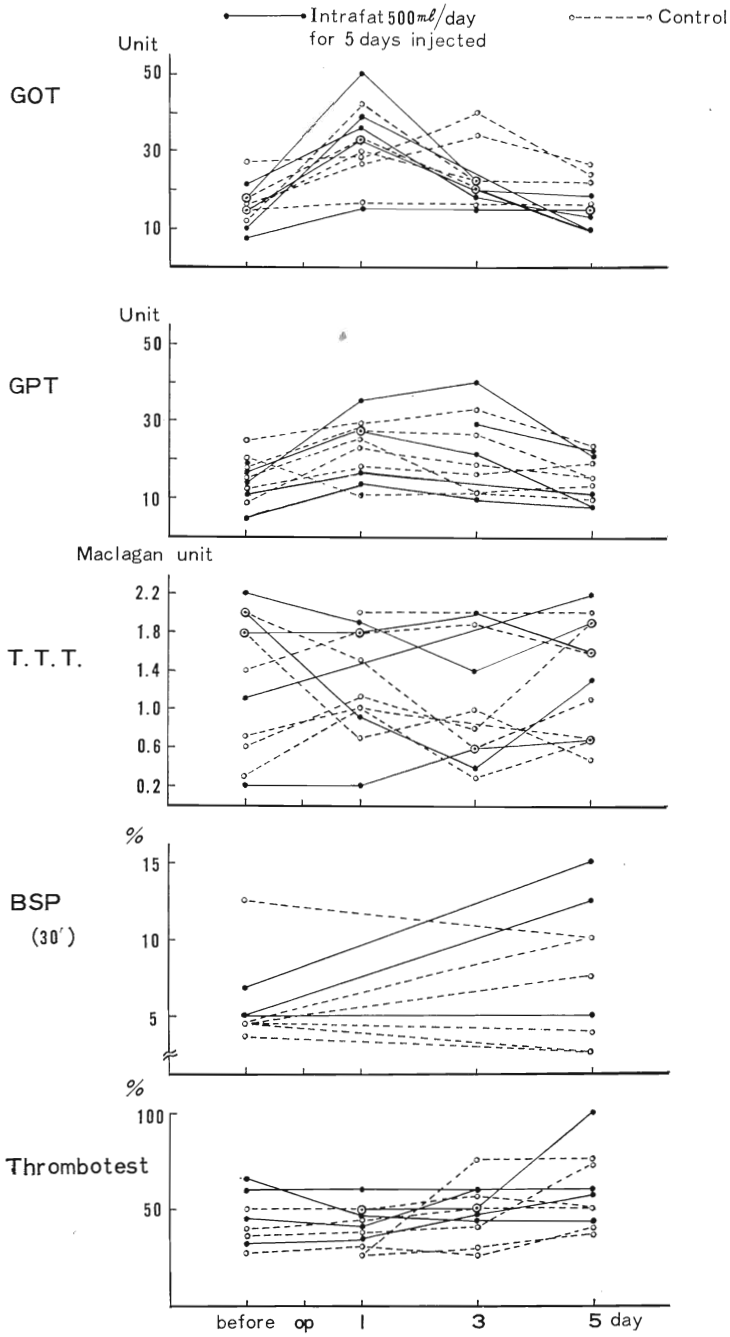

Fig. 10. The effects of intravenous fat infusion on GOT, GPT, TTT, BSP and Thrombotest.

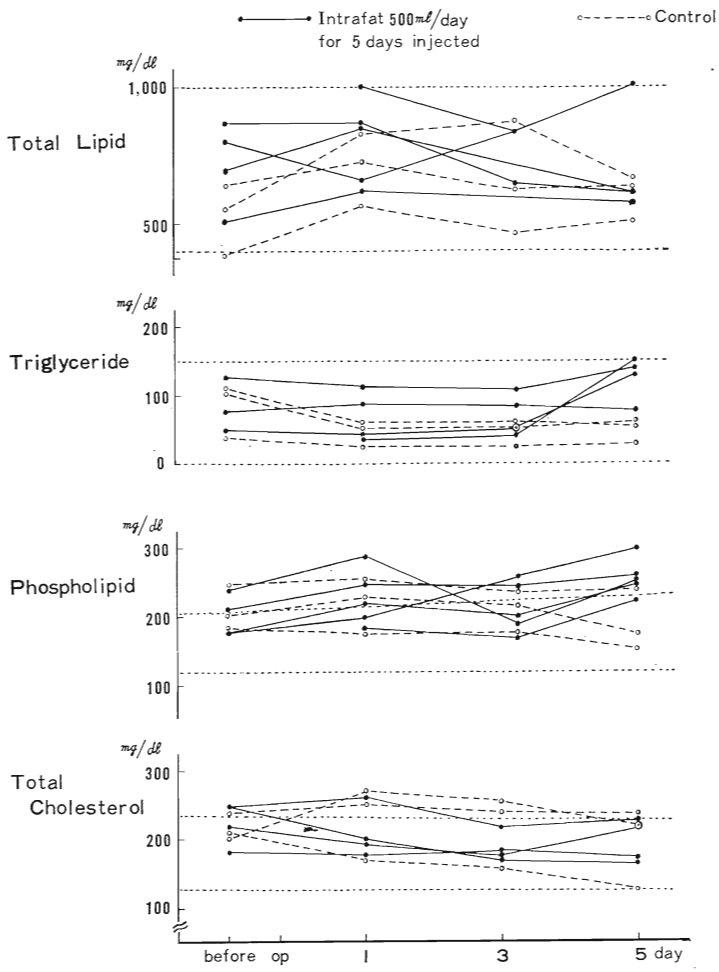

Fig. 11. The changes of plasma lipids following injection of fat emulsion. 500 ml of fat emulsion injected daily for five days.

when Menzel and Perco (1869)[4] introduced fat subcutaneously to cachectic patients with Pott's disease.

Holder[5] gave intravenous injections of milk and the first person who attempted to give artificial fat solutions intravenously was Yamakawa of Japan[6–10] who called his solution Yanol containing butterfat and cod liver oil. There are many reports on his experimental and clinical studies. Holt[11] made a solution of butterfat and cod liver oil, Narat[12] made an olive oil solution, McKibbin[13] produced a corn oil solution, Dunham[14] made a solution of olive oil and lard. All of these were fat emulsions of 3 to 10% but when clinical experiments were performed such side effects as fever,

nausea, jaundice, hemorrhage of the gastrointestinal tract, enlargement of the liver and spleen, respiratory distress, hypertension, etc. were noted during or after the injection. These overloading syndromes were so severe that question arose as to whether the fat was utilized or not, and hence this hindered the progress of research in this field to the degree that research came to a full stop until 1945 when Higasa[15] of Japan developed Fatgen made of sesame seed oil. Clinically the side effects were found to be not as severe during injection and after long usage were much milder than those with the other solutions. The obstacle was that an adequate amount of fat could not be administered and many patients developed a fever.

In 1957 Meyer[16] of the United States performed clinical studies with Lipomul and Lip Infonutrol. Although the side effects were minor, overloading syndromes were noted when used for a long time.

In recent years, Lipofundin made of cotton seed oil and soya bean phospholipids was developed in Germany and in France Lipophysan made of soya bean oil and lecithin was developed. In Sweden Intralipid made of soya bean oil and egg yolk lecithin was developed and put to clinical use. Schuberth[17] made different combinations of emulsions using different oils (olive oil, cotton seed oil and soya bean oil), different emulsifiers (saturated and unsaturated soya bean oil phospholipid and unsaturated egg yolk phospholipid) and different medias (glucose and glycerol). He proceeded to perform animal experiments with these emulsions, and as a result he observed that among the oils olive oil showed the strongest reaction in the human body followed by cotton seed oil, soya bean oil having the least reaction. Among the emulsifiers, those containing soya bean phospholipid showed the strongest reaction in the body with a decrease in blood pressure and respiratory arrest. Between the medias the body reacted to glycerol in a milder degree than glucose. In conclusion he reported that soya bean oil, unsaturated egg yolk phospholipid and glycerol were the best combination for fat emulsion because soya bean oil produced the least peroxide[18]. Even with this emulsion if administered in continuous doses exceeding 6 grams of fat per kilogram of body weight per day, diarrhea, respiratory distress and mild anemia were observed[19]. Schutteleworth[3] reports that when Lipomul (cotton seed oil and soya bean phospholipid emulsion) was administered continuously for 10–20 days an overloading syndrome consisting of headache, nausea, hepatosplenomegaly, anemia, jaundice, hemorrhage of the digestive tract, hyperlipaemia and disorders in coagulation appeared.

The toxicity of the emulsions, he believed, was caused by the low molecular triglycerides (tributyrin, trivalerine), which influenced the circulatory and respiratory systems, and lysolecithin, the peroxide of lecithin,

caused hemolysis. On the other hand, high molecule unsaturated fatty acids of vegetable oil origin contain very little toxic substances. According to Breinlich[20] an emulsion of soya bean oil and egg yolk phospholipids produced the least peroxide whereas cotton seed oil kept at room temperature produced peroxide immediately. Although the toxicity of an emulsion made from soya bean oil and egg yolk phospholipid was mild when kept at 40°C, the fat particles became swollen, the pH dropped and free fatty acids were released. When the fatty acid concentration exceeded over 15 mM, side effects were observed[21]. Wretlind[22] stated that phospholipids are one of the compositions of fat emulsion and is used as an emulsifier. When 9 grams of fat per kilogram per day were infused into dogs for 4 weeks with the phospholipid concentration between 0.6–0.8% no changes were noted in the blood phospholipid level although fatty degeneration of the organs was noted. On the other hand, if the phospholipid concentration was over 1.2% arise in the blood phospholipid level was noted but no fatty degeneration of the organs was observed and therefore it was possible to raise the concentration of the phospholipids.

When the emulsion is put to clinical use not only is the fat utilized for the production of calories but also it has indispensable nutritional values[23]. In this case the unsaturated fatty acids, especially linoleic acid, are essential for the function of the organs and as the composition of the body is able to nutritional solution with not only calories but containing optimal fatty acids[24].

Of the intrinsic and extrinsic fatty acids obtained from the diet or from the production of fatty acids, unsaturated fatty acid, linoleic acid in particular, suppress the glycokinase function, which is related to carbohydrate metabolism, and simultaneously acetyl Co-A carboxylase, and glucose-6-phosphate hydroxylase, which is related to fatty acid production. Hence there is an inhibition of synthesis from sugar to fatty acids. This is a biological result of the body trying to conserve sugar and obtaining its energy from fatty acids[25].

As mentioned above, the unsaturated fatty acids, linoleic acid in particular, play an important role. For this reason it is believed that this soy bean oil and egg yolk phospholipid emulsion is a nutritional solution with not only calories but containing optimal fatty acids.

Next the size of the fat particles became a problem. When the fat emulsion was given intravenously the best results were obtained when the size of the fat particles was less than 1.0 μ in diameter[26,27,11]. Higasa[15] states that when absorbed through the intestinal tract the size of the chylomicrons produced in the blood should be less than 0.5 μ in diameter. On the other hand, according to Sato if the fat particles exceeded 4 μ

pulmonary thrombosis occurred but there have been no reports on pulmonary thrombosis caused by Intrafat or Intralipid or Fatgen.

As forementioned, a fat emulsion of soya bean oil and egg yolk phospholipid has been reported to have the least side effects. The results with Intralipid when compared show that of the 2,781 cases given Intralipid in doses of 0.4–2.5 grams of fat per kilogram of body weight at the rate of 0.5 gram per kilogram per day, side effects during the injection were found to be shivering 1%, fever 2.7% and thrombophlebitis 1 case (Hellberg, Schuberth, and Wretlind[18]). Among our 108 cases given Intrafat (a total of 298 injections) in doses of 0.5–1.2 grams per kilogram of body weight per day at the rate of 0.5–0.6 grams of fat per hour, the side effects noted were shivering 0.1%, nausea 0.1%, and phlebitis 0.3%, showing that the side effects were the same or less. According to Jordal[28], thrombophlebitis with the use of fat emulsion occurred with a less frequent incidence that with the other solutions. With Intrafat thrombophlebities did occur though temporarily when the preparation had been refrigerated, as the preparation was low in temperature when the injection was given, resulting in a pure physical phenomena.

The soya bean oil and egg yolk phospholipid emulsions (Intrafat and Intralipid) administered over a long period of time had side effects as Hallberg[18] reported after administering Intralipid for 15 consecutive days in doses of 0.5–2.0 gram per kilogram per day. He stated that there was a temporary rise in the BSP values, a slight elevation of GOT, these being the only side effects. Neither an overloading syndrome nor a long term reaction was noted. In our study Intrafat was given for 10–15 consecutive days but neither anemia nor disorder of hepatic nor renal function was noted.

Conclusion

Experimental studies on Intrafat, a fat emulsion for intravenous infusion which was recently developed in our country, was conducted.

Results of both experimental studies on dogs and clinical investigations concerning the composition, side effects and toxicity are discussed. A comparative study on the literature on Intralipid was made. Further studies will be conducted on the metabolism of the administered fat, and the pathological findings and utilization will be presented in the next report.

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