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Effects of Parenteral Lipid Formulas on Seurm Lipids Clearance in Normal Volunteers

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ABSTRACT

Although intravenous fat emulsions are well accepted as a constituent of a total parenteral nutrition regimen, it is still controversial how much it can be used and who to use it in consideration of physical situation of useres. In this study, the effect of two marketed lipid formulas on serum lipids change was investigated. Each lipid formula was injected to twelve normal adult volunteers and a set of blood samples was drawn at 5 minute interval during the experiment. Changes of triglycerides, free fatty acids, free glycerol, total cholesterol and phospholipids in the serum were determined. To calculate serum lipids clearance, the pharmacokinetics of serum triglyceride, fractional removal rate(k) and half-life time(t/2), were calculated using intravenous fat tolerance-test(IVFTT). None of the parameters determined in this experiment was statistically different between two marketed formulas.

In summary, the bolus injection of the lipid formulas did not produce any adverse effects and their elimination kinetics from the blood stream were similar.

KEY WORDS : parenteral lipid formulas · serum Lipids change · fractional removal rate · half-life time.

Introduction

Parenteral nutrition is delivered via routes other than the alimentary tract, usually intravenously, when nutrient needs for patient cannot be met solely by enteral intake. Total parenteral nutrition (TPN) indicates that all necessary nutrients are being provided via veins ; either peripheral veins or a central vein can be used[1].

Adults who receive parenteral dextrose and amino acids but no fat develop biochemical essential fatty acid deficiency by the end of the second week[2]. If parenteral nutrition solutions containing only dextrose and amino acids are administered, patients typically develop fatty liver and cholestasis and have increased CO_2 production.

Nowadays, intravenous fat emulsions are acce-

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pted as a necessary constituent of a total parenteral nutrition regimen. The percentage of the fat emulsion related to the total energy supply should be 30~40% in a parenteral nutrition program. The main function of parenteral fat application is the supply of energy and essential fatty acids such as linoleic acid and linolenic acid.

Marketed parenteral fat emulsions are manufactured using soybean or safflower oil as fatty acid sources with egg lecithin added as an emulsifier. These products contain sufficient amount of linoleic acid and α-linolenic acid to cover the patient's nutritional needs. It has been shown that lipid calories are equivalent to glucose in the effect on protein balance since they have equal nitrogen sparing effect[3)4)].

There are metabolic and clinical advantages to the use of lipid calories in so far that liver fat and circulating insulin does not increase as much as with glucose. Furthermore weight increase is largely nitrogen related and not due to water and lipid accumulation, as with glucose. In addition, carbon dioxide production and respiratory minute volume are not affected as extensively as with glucose[5)]. Fat emulsions, however, cause a rise in serum lipids level such that it is contraindicated in patients with hyperlipemia, lipoid nephrosis, severe liver damage, and acute pancreatitis accompanied by hyperlipemia. Patients receiving fat emulsions should be observed for allergic reactions, hyperlipemia, hypercoagulability, nausea and vomiting, headache, flushing, dyspnea, fever, sweating, back or chest pain, and dizziness[6)]. The patient's liver function and ability to eliminate the infused fat from the circulation should be frequently monitored[7)].

The objective of the study was to compare the serum lipids clearance of two marketed lipid formulas, Lipovenös 10% and intralipos 10%, in normal volunteers using the intraveneous fat tolerance test(IVFTT)[8)] and other parameters.

Materials and Methods

The study was a double blinded, randomized, cross-over study with twelve normal, healthy, male volunteers(22~27 years of age)(Table 1). Subjects had no history of metabolic disorders especially hyperlipidemia and diabetes, or serious psychological, gastrointestinal, cardiovascular, hepatic, renal and/or hematological disease. Their body weights were normal(± 10%) for their heights according to the guidelines set forth in standard weight tables[9)]. Subjects had been ruled to be of good health following a physical examination, electro cardiogram(ECG) and medical history by registered physicians. An x-ray was required for subjects if they had not taken in the previous 12 months. The physician also reviewed preclinical laboratory test data from each subject.

Main compositional difference of two tested formulas was none except Intralipos contained less additives, such as glycerine(22.1g/ℓ vs 25.0g/ℓ) and tocopherol(0mg/ℓ vs 100mg/ℓ), when compare with Lipovenös.

Lipovenös 10% or Intralipos 10% solution was injected with dosage of 1.0mℓ/kg body weight. At 8 AM after overnight fasting, a catheter was introduced into an antebrachial vein of each arm, one for injection and the other for blood sampling. After about 10~15 minutes of rest in the supine position, 1.0mℓ/kg body weight Lipovenös 10% or Intralipos 10% was given as a single injection through one of the catheters according to the randomization schedule. The injection was given as

Table 1. Subjects data

	n	Mean± SD
Age(years)	12	25± 2
Weight(kg)	12	60± 6
Height(cm)	12	169± 5

fast as possible with a speed of approximately 1~2mℓ per second[10]. A set of blood samples was drawn from each subjects for determination of serum lipids before lipid formula injection, 5, 10, 15, 20, 25, 30, 35, and 40 mintes after injection. Changes of triglycerides, free fatty acids, free glycerol, total cholesterol, and phospholipids in the serum were determined by using test kit with principles of enzymatic or colorimetric method. Blood pressure and physical change were determined before and after lipid formula injections as vital signs. The pharmacokinetic of the variable triglyceride has been calculated as a pure evasion kinetic from time point 5 minute to time point 40 minute on the basis of an 1-compartment model [11]. Calculation have been performed with the programs PKCALC[12] and SYSTAT(Modul nonlinear fitting).

The subjects were crossed over to receive the alternate lipid emulsion one week later under identical fasting and study conditions.

A comprehensive descriptive analysis was performed for all data collected in the case report forms. Depending on the level of measurement, minima and maxima, means and standard deviations were computed separately for each test parameter. Differences in the laboratory parameters were tested for statistical significance between the medication conditions using multiple factor repeated measures analyses of variance[13]. All tests were performed with a type A error of 5% (two-sided). All calculations were performed with the statistical software package SPSS/PC.

Results and Discussion

The volunteers in the Lipovenos 10% treatment group showed a mean decrease of 4mmHg of systolic blood pressure, whereas the volunteers in the Intralipos 10% treatment group showed a mean increase of 3mmHg as shown in Table 2. These changes, however, were not statistically significant by paired t-test. With diastolic blood pressure, the volunteers in the Lipovenös 10% treatment group showed a mean decrease of 2mmHg, whereas the volunteers in the Intralipos 10% treatment group showed a mean increase of 2mmHg. These changes were not statistically significant. Therefore, there were no changes between two treatment groups in both blood pressures as an indicator of vital sign during the experiment.

In both treatment groups, level of plasma triglycerides was increased immediately after injection and then the values were continuously decreased from 5 minutes to 40 minutes after injection as shown of Fig. 1. This effects by time was statistically significant with multivariate analysis of variance($p \leq .001$). There was, however, no statistically significant difference between the two treatment groups with treatment by time effect.

Changes of plasma free fatty acids in both treatment groups showed increase immediately after injection which reached its maximum 10 minutes after injection as shown on Fig. 2. From 10 minutes to 40 minutes after injection there was a slow decrease. This effect by time was statistically sig-

Table 2. Changes of blood pressure before and after the experiment (n=12, mmHg, mean± SD)

	Systolic blood pressure		Diastolic blood pressure	
	Lipovenös	Intralipos	Lipovenös	Intralipos
Initial	124± 7	119± 7	74± 4	70± 5
Final	120± 8	122± 11	72± 11	72± 8

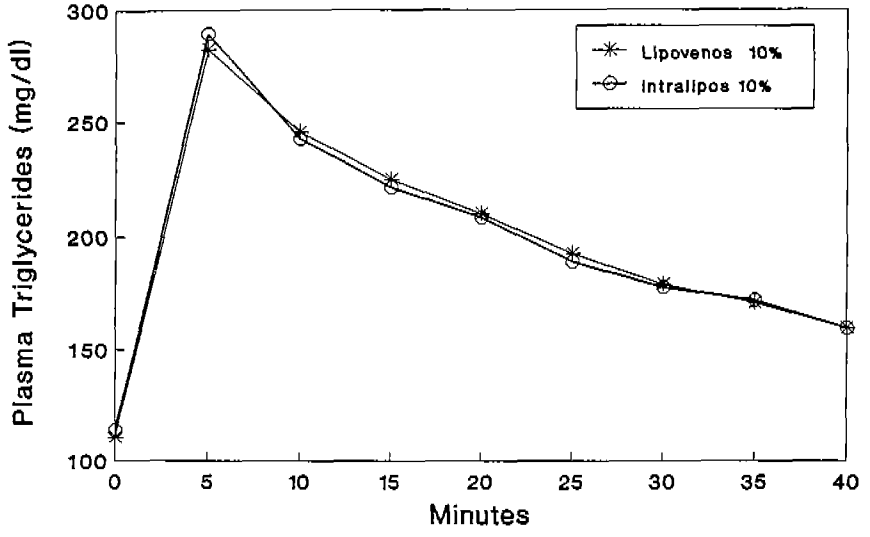

Fig. 1. Change of plasma triglycerides during the experiment.

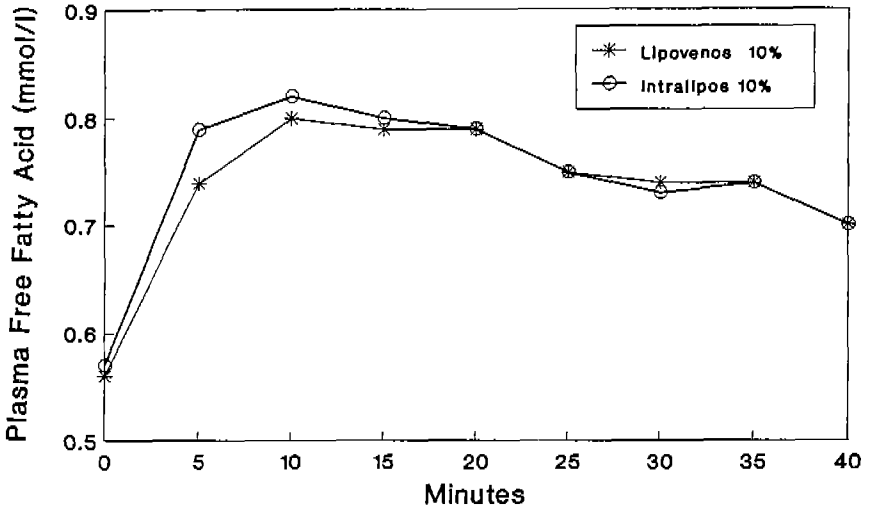

Fig. 2. Change of plasma free fatty acid during the experiment.

nificant(multivariate analysis of variance, $p \leq 0.01$), however, no statistically significant difference was observed between the two treatment groups with treatment by time effect.

Changes of plasma total cholesterol in both treatment groups showed on Fig. 3. There was a decrease immediately after injection followed by an up and down of mean values from 5 minutes to 40 minutes after injection. This effect by time is not statistically significant. There is also no statistically significant difference between the two treatment groups with treatment by time effect.

Changes of plasma free glycerol, as shown on Fig. 4, were increased immediately after injection which reached its maximum 5 minutes after injec-

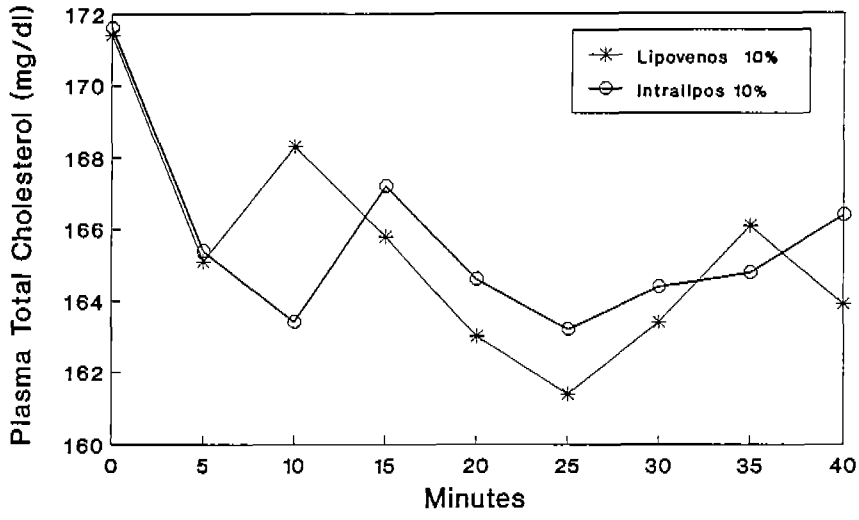

Fig. 3. Change of plasma total cholesterol during the experiment.

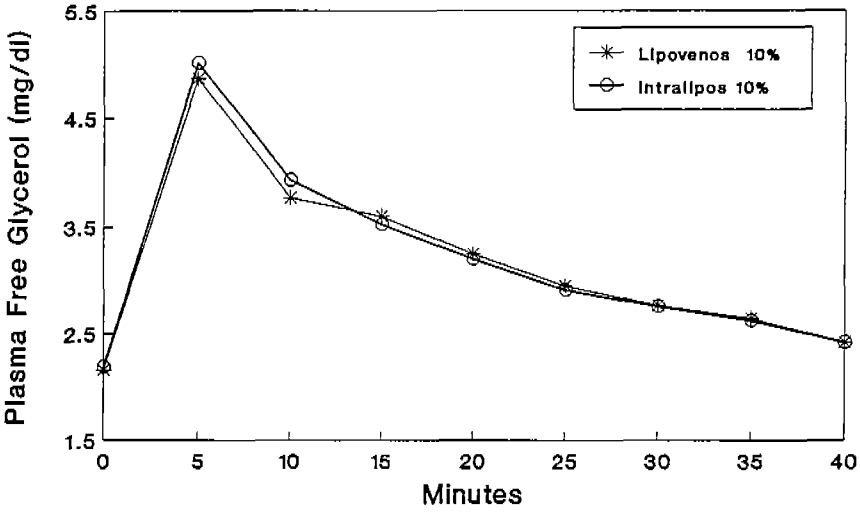

Fig. 4. Change of plasma free glycerol during the experiment.

tion. From 5 minutes to 40 minutes after injection there was a continuous decrease. This effect by time was statistically significant(multivariate analysis of variance, $p \leq 0.01$). There was, however, no statistically significant difference between the two treatment groups with treatment by time effect.

The mean values of phospholipids in both treatment groups, as shown on Fig. 5, were increased immediately after injection which reached its maximum 10 minutes after injection. From 10 minutes to 40 minutes after injection there were only slight changes. This effect by time was not statistically significant. There was also no statistically difference between the two treatment groups with treatment by time effect.

Pharmacokinetic calculation of serum triglyceride clearance of two formulas is shown in Table

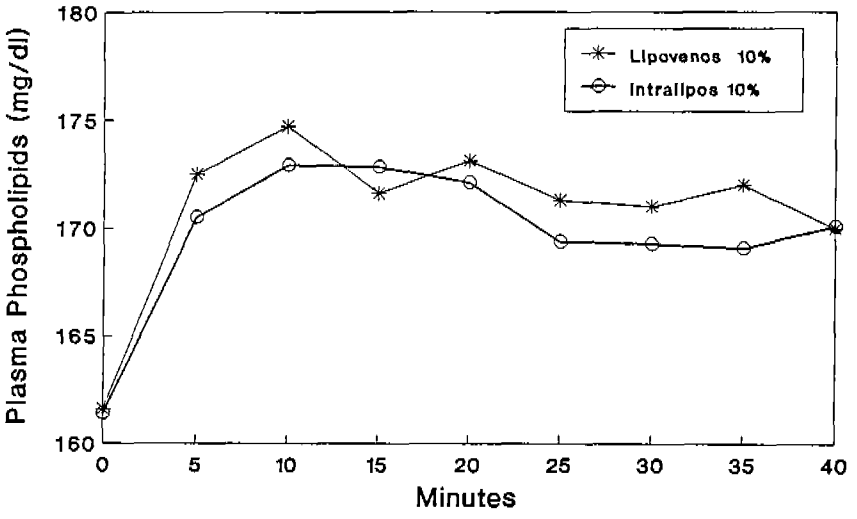

Fig. 5. Change of plasma phospholipids during the experiment.

Table 3. Pharmacokinetic calculation of serum lipid clearance (n=12, mean± SD)

Parameter	Lipovenös 10%	Intralipos 10%
t/2(min)	20.01 ± 6.97	18.46 ± 7.41
$k_2(min^{-1})$	0.0404± 0.0200	0.0444± 0.0214

3. In this study, the fractional removal rate k and the half-life time t/2 of two differerent fat emulsions were randomly compared using the intravenous fat tolerance test(IVFTT) in male volunteers. The clearance k and t/2 were statistically similar regardless of the formulas injected, so that both emulsions showed similar serum lipids clearance behaviour. These k values were comparable to those reported for Intralipid in healthy subjects [14)17)]. The increase of the serum triglyceride of soybean oil based emulsions has been controversially postulated to accelerate the clearance in animals[18)] or to be without effect in humans[19)].

In conclusion, the bolus injection of the two different emulsions did not produce any adverse effects and their elimination kinetics from the blood stream and serum lipid changes were statistically similar.

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= 국문초록 =

지질 수액체 투여가 정상인의 혈장 지질변화에 미치는 영향

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Total parenteral nutrition(TPN)의 구성성분으로써 지방질 수액제의 사용은 점차 많아지고 있지만 사용량이나 사용대상에 대해서는 아직도 규명해야 할 것이 많다. 본 연구에서는 시판 지방질 수액제들을 사용했을 때 이들이 혈청 지질변화에 어떠한 영향을 미치는가를 비교검토하였다. 각각의 시판 지방질 수액제를 12명의 정상적인 사람에게 주사한 후 5분 간격으로 혈액을 채취하여 혈청내 각종 지질의 변화를 관찰하였다. 혈청내에서 지질이 감소되는 속도를 계산하기 위하여 혈청중 중성지방의 fractional removal rate(K)와 반감시간(t/2)를 intravenous fat tolerance test(IV-FTT)를 사용하여 계산하였다. 측정한 각종 항목에서 두 시판 지방질 사이에 통계적 차이를 볼 수 없었으며 어떤 부작용도 관찰되지 않았다. 또한 두 제품 모두 혈액중의 지질감소 속도가 유사하였다.