

Effect of clofibrate on serum triglyceride and cholesterol after intravenous lipid in very low birth weight neonates

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ABSTRACT

Background: Lipoprotein lipase activity can be increased by clofibrate. Clofibrate is used to reduce serum triglyceride level in adults. The aim of this study was to determine the effect of clofibrate on serum triglyceride and cholesterol level after administration of intravenous lipid in very low birth weight neonates.

Methods: In a randomized double blind placebo – controlled study, 60 very low birth weight neonates were elected. They received intravenous lipid for parental nutrition. Study participants (case) received one dose clofibrate 100 mg.kg orally. Control group received sterile water for placebo as volume as clofibrate. Serum triglyceride and cholesterol levels were measured in first and fifth days after starting of intravenous lipid (one day after intervention).

Results: Two groups were the same in sex, birth weight, gestational age and mode of delivery. There were no significant difference between the clofibrate and control groups in mean total serum triglyceride and cholesterol levels at before and after drugs administration (P=0.20 and 0.40 respectively).

Conclusion: This study showed although clofibrate has been reduced serum triglyceride levels in adults but it has not effect on serum triglyceride and cholesterol levels in very low birth weight neonates who use intravenous lipid.

Keywords: Clofibrate, very low birth weight, triglyceride, Parental Nutrition

Introduction

Clofibrate is an activator of peroxisome proliferators-activated receptors. It decreases serum cholesterol and triglyceride levels and has been used for many years as an effective hypolipidemic agent in adults (1, 2). Clofibrate is also a glucuronosyl transferase inducer and can increase bilirubin conjugation and excretion (3-10). A single dose of clofibrate (100 mg.kg) has been proposed for the prevention and treatment of neonatal hyperbilirubinemia (5-10). Clofibrate in adults when used as an antilipidemic agent has some side effects such as nausea, gastrointestinal disturbances, vomiting and loose stool. Other possible complications are muscle cramps, fatigue, pruritus, and alopecia (5). In the neonatal study with a single high dose of clofibrate none of these side effects were reported (7, 8, 9, and 10). Cholesterol is a necessary element of cell membranes, indeed mother milk include 10-15 mg.dl of cholesterol. Normal value of cholesterol is related to age and sex and increases with age (11). Intra venous lipid (IVL) not only is necessary for preventing fatty acid deficiency in very low birth

weight (VLBW) neonates but also it has prominent effect on obtaining enough energy and weight gaining. IVL has been made by 10, 20, 30% emulsion (12). Antilipolytic effect of clofibrate is related to inhibition of AMP cycle by Adenil cyclase inhibitors (13). Several derivatives of fibric acid are known to reduce concentrations of plasma triglycerides (PTG). One relatively new agent in this group is clofibrate (14). Clofibrate seems to be effective in reducing the plasma lipid concentrations in patients with endogenous (or carbohydrate- induced) hypertriglycemia. If hypertriglycemia has a cause relation to coronary artery disease, clofibrate may be of value for the prevention and treatment of this problem (15). However no research has been found that surveyed the effect of clofibrate on PTG and cholesterol of neonates so in this study we determined the effect of clofibrate on PTG and cholesterol of VLBW infants who received Intralipid solution for parental nutrition.

Material and Method

In a randomized double blind controlled-

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placebo trial 60 very low birth weight neonates who were admitted to Neonatal intensive care unit (NICU) elected. Written consent was provided from each patient's parents and the study was approved by the University Ethical Committee. The inclusion criteria were preterm neonates with birth weight less than 1500 grams who received intravenous lipid (IVL) for parenteral nutrition. The exclusion criteria were the presence of any congenital anomaly, hemolytic disease (Rh or ABO incompatibility and a positive Coombs' test), hyperbilirubinemia, Infection (congenital or acquired), dehydration, G6PD deficiency, and a history of Phenobarbital intake either by Mother or infant. The clinical examination, sex, birth weight, gestational age and mode of delivery were recorded. All infants in this study were examined by a neonatologist during hospitalization and two days after discharge in the outpatient clinic for evaluation of any side effects of the drug. After consent of parents, babies randomly were divided in two groups. The infants in the colfibrate group (n=30) received a single oral dose of clofibrate, 100 mg.kg, while the control group (n=30) received distilled water in an equal amount and color as placebo by orogastric tube. In 2th days of life 10% intralipid 1g.kg were started for all neonates and 0.5 g.kg were increased daily until 2.5 g.kg.d. Indeed routine lab test that were done for all neonates, triglyceride and cholesterol were checked in first and fifth day (one day after intervention) after IVL therapy. In fourth day of life 100 mg. kg clofibrate were given to clofibrate group. Liver function tests (SGOT, SGPT) were checked finally. Data were analyzed with SPSS version 11.5. Numerical variables were compared between the Control and clofibrate groups using the independent Student's t-test. The χ^2 and Fisher exact tests were used to compare categorical variables between two groups. P values of <0.05 were considered statistically significant.

Results

Two groups were the same in sex, birth weight, gestational age and mode of delivery table 1. Also frequency of diseases such as intraventricular hemorrhage, intrauterine growth retardation, respiratory distress syndrome and sepsis were controlled in two groups. There were no significant differences about disease in two groups.

No significant difference was observed between two groups in mean triglyceride in the first day and fifth day of study (p=0.198). Also there was no

significant difference between mean serum cholesterol in the first day and fifth day of study in two groups (Table 2). Result shows no significant difference in mean first day and 5th day triglyceride in male and female (p=0.27) and (p=0.11) respectively. Mean cholesterol level in first day showed no significant difference between two group while there was significant difference between two group in fifth day of study p=0.24 and p= 0.04 respectively (table3). On serial examinations during hospitalization and on the second and seventh days after discharge no drug side-effects were observed.

Discussion

It has been shown that infants on fat-free parenteral nutrition develop plasma lipid changes and essential fatty acid deficiency within a week. Fat emulsions in general have added greatly to the efficiency of intravenous nutrition. Advantages include the ability to give large amounts of energy in a small, isotonic volume; to give essential fatty acids for prevention of essential fatty acid syndrome; and to give total parenteral nutrition by either the peripheral or the central route. There are currently a number of 10% and 20% fat emulsions in the market, two of which Intralipid and Liposyn are most widely used. The major difference between these two products is that Intralipid has a soybean oil base and contains some linolenic acid, and liposyn has a safflower oil base and contains only trace amounts of linolenic acid. Linolenic acid is potentially necessary for the human species, therefore liposyn appears to produce a higher level of serum triglyceride in infants. Intercurrent illness may cause hypertriglyceridemia in any infant in whom previous fat tolerance had already been established. Long term parenteral nutrition in infants seems to lead to elevation of triglycerides perhaps because of the lack of carnitine in intravenous solution. The use of steroids and aminophylline in chronically ill infants seems to add to hypertriglyceridemia.

Evaluation of triglycerides and free fatty acids will occur if the infant's ability to metabolize fat is increased. This may be due to a developmental insufficiency of lipoprotein lipase or its activator. Monitoring of triglyceride levels is important; measurement of free fatty acids also is available but takes longer. Serum cholesterol level will rise partly because of infusion and partly because of endogenous production. It should be monitored periodically. Excess lipid may be harmful because lipoprotein lipase enzyme is low in very low birth

weight neonates, results delay in lipid clearance and hypertriglyceridemia. Serum triglyceride should be checked with intra venous lipid infusion. Especially with 10% intralipid, because if phospholipid to triglyceride ratio is more than 20% intralipid, it may affect the triglyceride clearance. Infusion rate should be 0.15 mg.kg.h and serum triglyceride must maintain at 150 to 200 mg.l. Some studies reported that clofibrate is effective in reducing the plasma lipid concentrations in patients with hypertriglycemia in adult (13, 14). Adams Also suggest that clofibrate reduces serum triglyceride during 6 hours. So far, there has been no study to determine the effect of clofibrate on triglyceride in neonates. Our results show that clofibrate does not have any significant effect on serum triglyceride and cholesterol level in Very Low Birth Weight (VLBW) neonates.

Adams also demonstrated that by inhibition of one or more reactions in esterification of sn-glycerole-3-P, clofibrate induces hepatic glycerolipid synthesis reduction (2).

Some studies show that clofibrate has no effect on triglyceride and cholesterol when they are in normal range (12). Consistently in this study the range of cholesterol and triglyceride were normal before and after intervention. So according to previous studies, it has no significant effect on their changes. In case group after clofibrate administration, two case developed with metabolic acidosis and one case developed diarrhea that was resolved in follow up visits after treatment. Primary and secondary level of triglyceride and cholesterol in male and female were in normal range although in females the levels were slightly higher than males. This finding is confirmed by other studies (11). D'costa suggested that suppression of AMP production by inhibition of adenylate cycles is the action of clofibrate in reduction of placema lipid concentration. This antilipolytic action may partially be due to deprivation of liver from free fatty acid substrate for lipoprotein synthesis (13). Therefore in Low Birth Weight preterm newborns, clofibrate would not decrease placema lipid. Kesaniemi indicated that clofibrate reduced 32% placema total triglyceride and 38% VLDL triglyceride. As we use clofibrate therapeutically in one dose (3-10) antilipidemic effect of clofibrate did not appear in newborn.

To Sum it up, triglyceride and cholesterol serum in neonates using intralipid 10% with speed less than 2 mg.kg.h is maintaining in normal range, so therapy is not required. The important

finding of this study was that clofibrate has no significant effect on triglyceride and cholesterol level in neonates when they were in normal range. So although clofibrate in adult hypertriglyceridemia cause decrease in triglyceride (1, 2) and cholesterol serum, in LBW neonates it has not significant effect.

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Table1. Characteristic of newborn in clofibrate and control groups

Item	Control NO=30	Clofibrate NO=30	P value
male n (%)	14(46.7)	14 (46.7)	1
Birth weight (gm) mean ± SD	1171.67 ± 179.35	1212.33± 248.73	0.471
Gestational age (week) mean ± SD	30.8 ± 2.67	30.43 ± 2.42	0.579
mode of delivery (cesarean section) n (%)	19(63)	17(57)	P=0.92

Table2. Triglyceride and cholesterol level before and after intervention

	Control group (n = 30) Mean ± SD	Clofibrate group (n=30) Mean ± SD	P value
1 th triglyceride	61.23±25.71	96±50.13	P=0.20
2 nd triglyceride*	92.84±48.55	110.5±33.05	
1 th cholesterol	92.2±30.86	93.97±38.58	P=0.40
2 nd cholesterol*	127.4±42.45	138.38±52.31	

Table2. Triglyceride and cholesterol according to sex

	male (n = 30) Mean ± SD	female (n =30) Mean ± SD	P value
1 th triglyceride	72.1±40.03	123.97±34.99	P=0.27
2 nd triglyceride	95.44±37.17	134.45±120.13	P=0.11
1 th cholesterol	87.43±32.22	98.03±35.37	P=0.24
2 nd cholesterol	119.82±43.55	144.32±46.02	P=0.04

