Ethyl-2-(*p*-chlorophenoxy)-2-methylpropionate (Clofibrate) in Experimental Fat Embolism in Rats (35193)

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Fat embolism is a syndrome in which the intravascular fat appears as globules large enough to occlude capillaries and not in the fine emulsion of a lipemia (10). It is a major cause of morbidity and mortality in patients sustaining skeletal and soft tissue trauma (6). Fat embolism is a pulmonary disease (10), and neutral fats and free fatty acids (FFA) are the etiologic agents (2, 10). The treatment of fat embolism in patients includes the intravenous administration of alcohol (7), intravenous fluids (10), corticosteroids (1, 10), and oxygen (10, 13). However, no drug therapy is generally used for the disturbed lipid state. Ethyl-2-(*p*-chlorophenoxy)-2-methylpropionate (clofibrate) is known to lower FFA and triglyceride levels (3) and its use in the treatment of fat embolism has been suggested (9).

This study was undertaken to determine the value of clofibrate in the treatment of experimental fat embolism in rats.

Methods. Two hundred eight male Sprague-Dawley rats weighing 200–220 g were used (Table I). Fat embolism was produced by the intravenous injection of 0.04 ml of oleic acid (purified, low polyunsaturated grade, Fisher Scientific, Fair Lawn, N.J.); or 0.15 or 0.20 ml of triolein (substantially free of oleic acid, Sigma Chemical Co., St. Louis, Mo.). Oleic acid and triolein were stored in the refrigerator and brought to room temperature prior to injection. Treated animals were given 10 mg/kg of clofibrate (Ayerst Laboratories, New York, N.Y.) intravenously 24 hr prior to the intravenous injection of oleic acid or triolein. Groups VI and VII were given, in addition, clofibrate (20 mg/kg) daily following fat embolism. The surviving animals were sacrificed after 96 hr with intraperitoneal pentobarbital and the lungs were removed immediately for histologic preparation. Staining of sections with hematoxylin and eosin or oil red O was done.

Results. Results of the experiments are displayed in Table I. None of the saline or clofibrate-injected controls died. The animals injected with oleic acid either died within 3 hr, or survived the experimental period. Clofibrate did not improve the survival of animals injected with oleic acid. In animals injected with 0.2 ml of triolein and treated with clofibrate (Group VIb) there was an increase in deaths compared with animal sinjected with 0.2 ml of triolein only (Group Vb). The deaths in groups of triolein-injected animals occurred later than those in oleic acid-injected animals. No difference between triolein-injected ainmals (Group Va, VIa, and VII) was noted.

Histologic examination of animals injected with oleic acid occasionally demonstrated oil red O positive material in the alveolar wall, which might be due to the synthesis of triglycerides from FFA in the lung tissue (5). All animals injected with oleic acid (Group III and IV) showed perivascular hemorrhage, alveolar wall thickening, and atelectasis. Animals dying soon after oleic acid injection also had pulmonary edema. The lungs of triolein-injected ainmals (Group V, VI, VII) contained abundant intravascular oil red O stained fat emboli. Edema, hemorrhage, and atelectasis were focal and not so severe as in the animals injected with oleic acid.

Discussion. The mechanism of action of clofibrate is not known. Clofibrate binding to anion binding sites on proteins (12) has been postulated but this is still in doubt (8). Barrett and Thorp (3) suggested that relative enhancement of glycolysis occurs with

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TABLE I. Experimental Fat Embolism in Rats.

Group	Material injected	No. of animals	Survivals	Deaths
I	Saline	14	14	0
II	Clofibrate, 10 mg/kg	16	16	0
III	Oleic acid, 0.04 ml	29	12	17
IV	Oleic acid, 0.04 ml; clofibrate, 10 mg/kg	39	16	23
Va	Triolein, 0.15 ml	22	22	0
b	0.20 ml	15	8	7
VIa	Triolein, 0.15 ml; clofibrate, 10 mg/kg	21	21	0
b	Triolein, 0.20 ml; clofibrate, 20 mg/kg daily	11	2	9
VII	Triolein, 0.15 ml; clofibrate, 20 mg/kg daily	41	41	0

indirect lowering of FFA levels. Clofibrate is known to lower the plasma FFA levels of rats (3), and humans (12), and dogs (3). However, no improvement of the survival rate of histologic appearance of the lungs was seen in our oleic acid-injected animals.

Serum triglyceride levels will decrease in response to clofibrate (4). The depressant effect of clofibrate is greater on low-low density lipoproteins (S_f 20–400) rich in triglycerides as compared with low density lipoproteins (S_f 0–20) rich in cholesterol (11). Human accident victims treated with clofibrate have decreased serum lipid levels and associated clinical improvement (9). The decreased survival in triolein-injected animals (Group VIb) was probably due to clofibrate competition for protein binding sites, thus elevating the FFA levels with subsequent lung damage.

Summary. 1. Clofibrate as a therapeutic agent in experimental fat embolism in rats was evaluated.

2. Survival of animals injected with oleic acid was not affected.

3. Survival of animals injected with triolein decreased.

4. Under the conditions of this experiment the value of clofibrate as a therapeutic agent for experimental fat embolism was not substantiated.

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