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Myopathy induced by clofibrate treatment in normolipaemic patients

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On the basis of the occurrence of myopathy in a clofibric acid treated child with diabetes insipidus, three other children with the same disease were examined in order to find indications for a myopathic side-effect of the drug. When the children were found to have increased creatine phosphokinase activity and EMG changes, two of the authors took clofibric acid themselves. In both test persons subclinical myopathy was produced. After stopping the drug, transitional hypertriglyceridaemia occurred. These side-effects should serve as a warning of an uncritical application of clofibric acid and its esters.

Clofibrate and clofibric acid are widely used for the treatment of hyperlipoproteinaemia types IIb and IV [8]. In the pertaining literature [e.g. 9, 15, 16, 21, 22, 23, 25, 47] side-effects of these drugs were scarcely ever mentioned.

Recently, clofibrate has been used in patients with diabetes insipidus because of its antidiuretic effect. This effect is said to be due to an increased production of ADH by the supraoptic nucleus and the posterior pituitary.

In 1976, we have reported on myopathy during clofibric acid treatment in a patient suffering from diabetes insipidus [4]. The changes of serum lipids, the increase of serum creatine phosphokinase (Fig. 1) and aminotransferase levels observed in that case have induced us to examine other patients subjected to clofibric acid treatment. As our suspicion of the myopathy inducing effect of clofibric acid was strengthened, two of the present authors subjected themselves to clofibrate treatment. The present paper reports on these observations.

Results

I. Observations in patients

In all the patients treated with clofibric acid, an increase in the serum creatine phosphokinase (CPK) level was noted and one patient developed myalgia. The highest CPK value was found in a patient 5 weeks after beginning the treatment, in another patient after 18 weeks and in a third one, a 7 years old girl, after 12 weeks. In a boy 11 years of age who had no clinical complaints, after 14 days treatment CPK values of 5000 U/l were registered (Fig. 1). After discon-

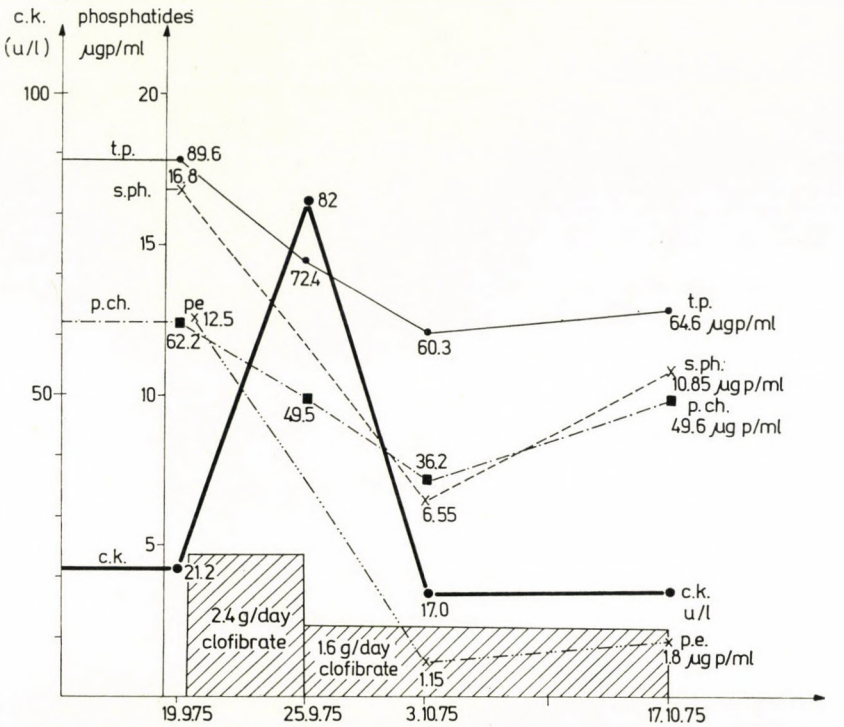

FIG. 1. Creatine phosphokinase activity and serum phosphatide concentrations in a patient treated with clofibrate for diabetes insipidus (patient K. E. — after reapplication of clofibrate, the treatment with which had been stopped before a fortnight) (4) c. k. = creatine phosphokinase; p. e. = phosphatidyl-ethanolamine (ethanolamine cephalin); s. ph. = sphingomyelin; p. ch. = phosphatidyl choline (lecithin); t. p. = total phosphatide (Unit of phospholipid concentrations g P/ml)

tinuing the treatment, CPK activity became normal in every patient. The increase in serum CPK was associated with an increase of the aminotransferase level, so that the serum glutamic oxalacetic transaminase (SGOT)/ serum glutamic pyruvic transaminase (SGPT) quotient amounted to 1.5.

Examinations of serum lipids could only be carried out in two patients, as in all the others the increase of CPK values made us to discontinue the therapy. In the first patient, the increase in serum CPK coincided with the greatest decrease per unit of time of phosphatidyl-ethanolamine, sphingomyelin and phosphatidyl choline. In the other (J. S.) patient the lipid concentrations showed no significant changes.

The electromyogram of the left thenar muscle of the patient (J. S.), who had been treated longest, revealed a myopathic pattern.

In the same patient, 0.05 kg body weight of succinyl choline injected in a distal vein caused instead of an increase a decrease in the serum phosphatide fractions (Fig. 3), due to the evoked muscle spasm [36].

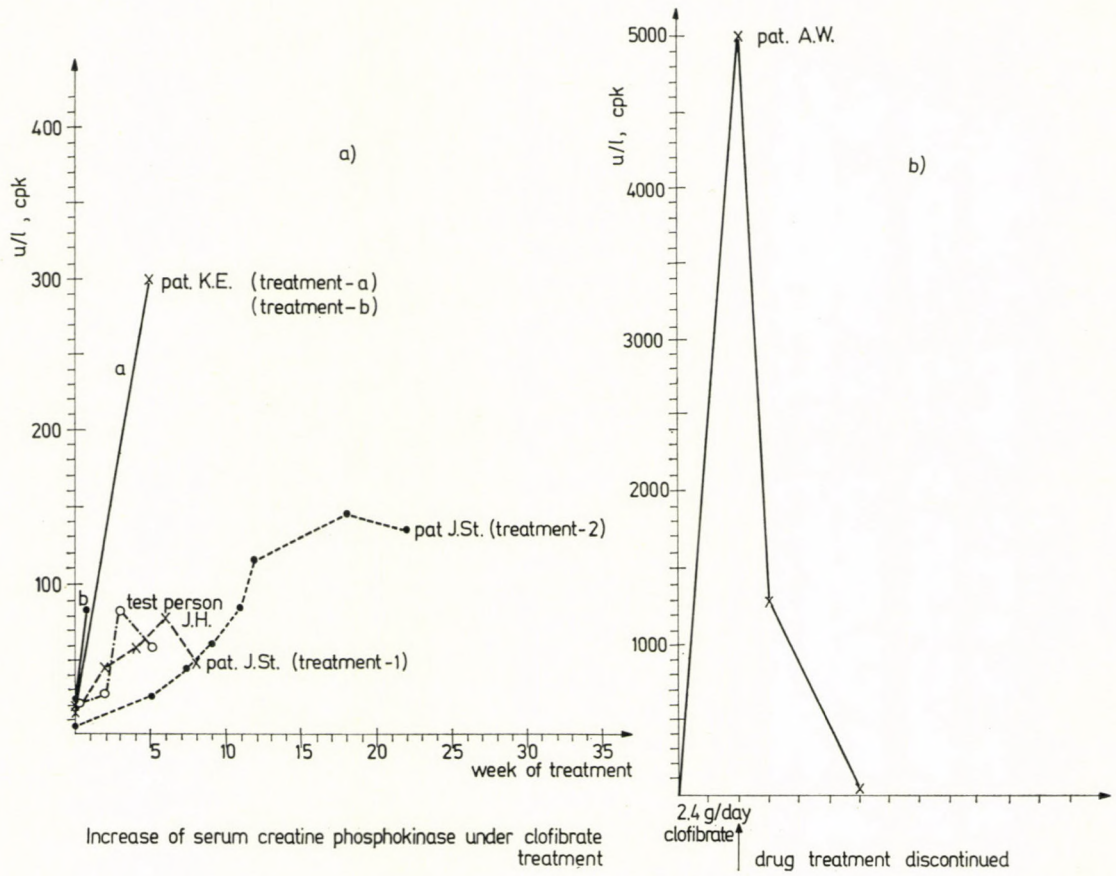

FIG. 2. Serum creatine phosphokinase level in 3 patients and a test person

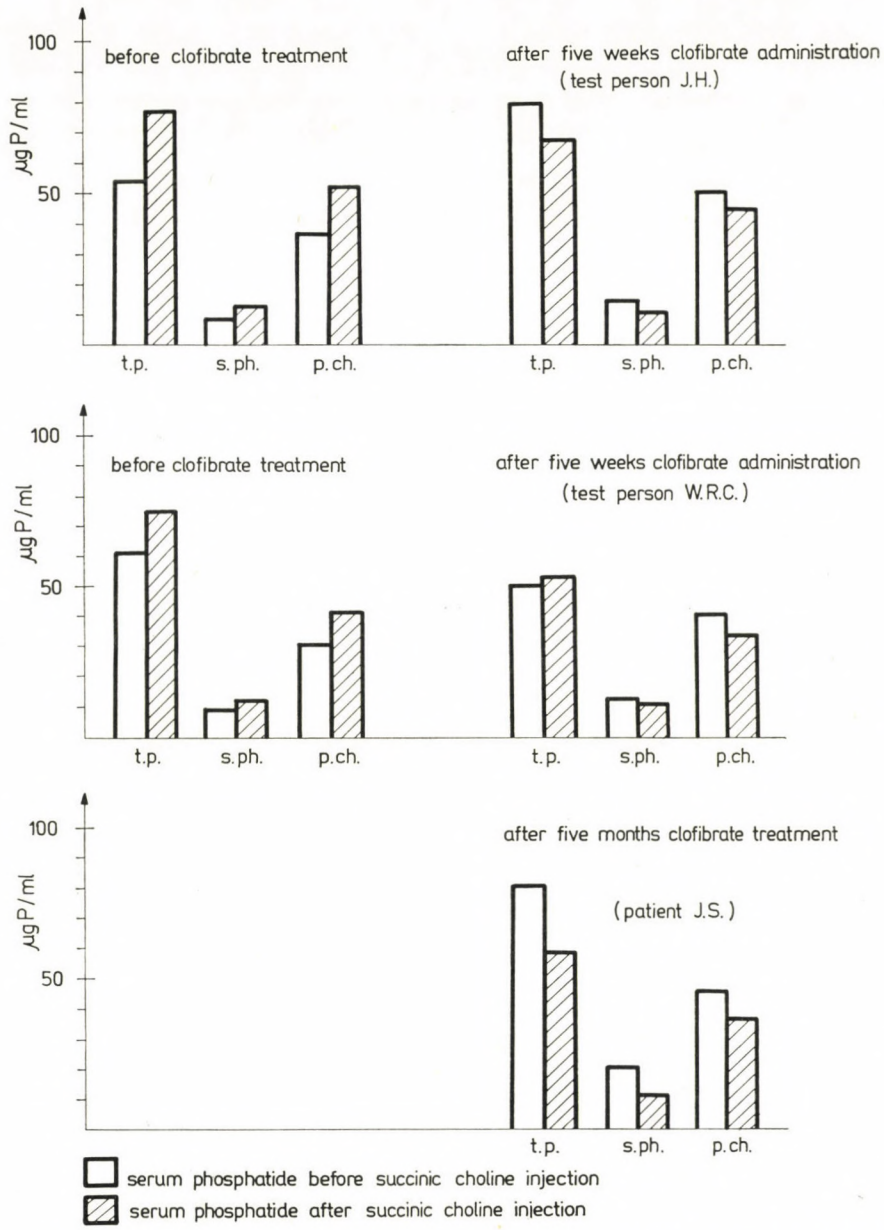

FIG. 3. Effect of clofibrate treatment on the result of succinyl choline provocation tests; serum phosphatide choline before and after injection of succinyl choline (0.05 mg/kg body weight)

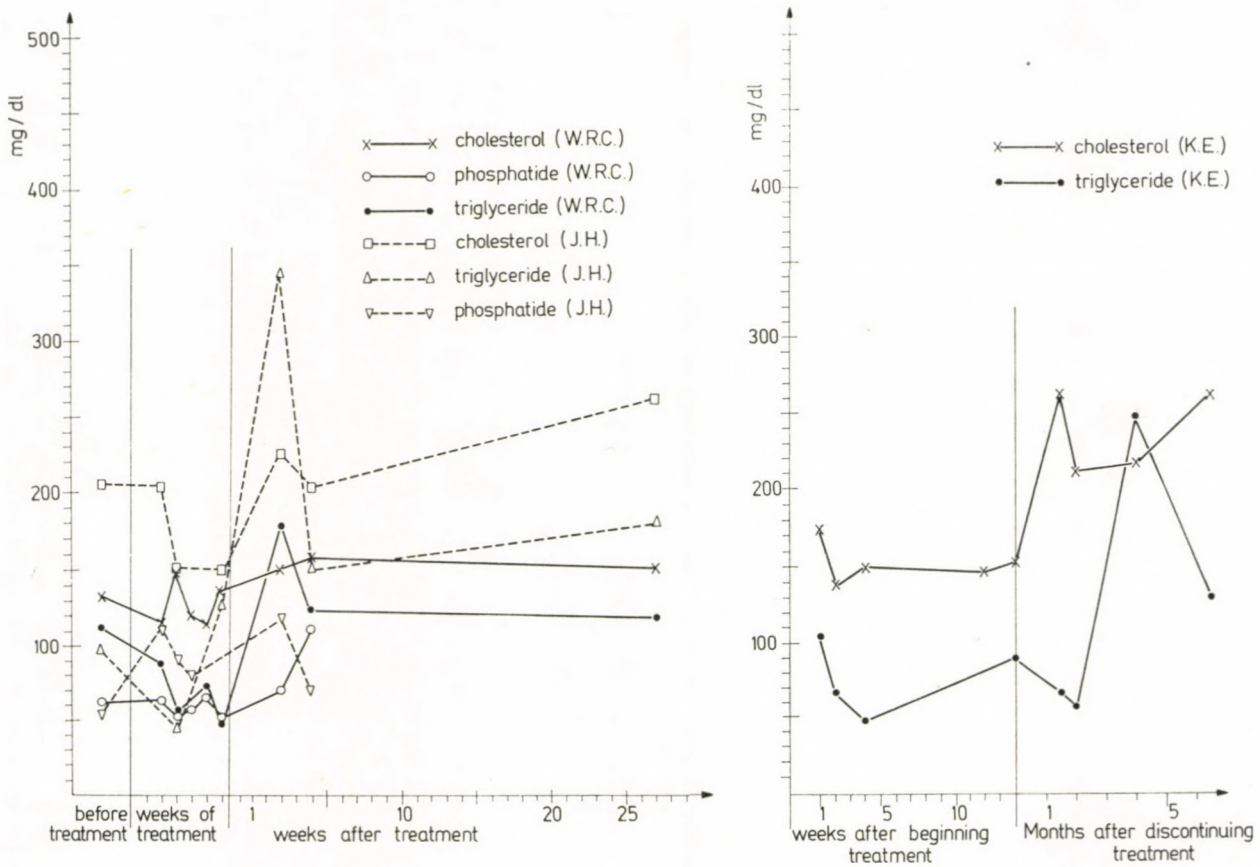

FIG. 4. Serum lipid concentrations after stopping clofibrate treatment

II. Observations in control subjects

Both volunteers (healthy normolipaemics, 32 and 34 years old) took 2.4 g/day of clofibric acid for five weeks. In their serum and erythrocytes, creatine kinase, aminotransferase, calcium, serum phosphatide, free fatty acid, triglyceride, cholesterol, as well as the phosphatide levels were regularly determined.

In order to record the development of a drug-induced myopathy, we made electromyograms (EMG) before treatment and after a five-week course of clofibrate. In addition EMGs of the left thenar muscles were made before and after injection of 0.05 mg succinyl choline/kg body weight into a distal vein after arterial obstruction with a blood pressure cuff on the left forearm. Succinyl choline provocation is regarded as a sensitive test of membraneous injuries of the muscles, and used to seize patients prone to malignant hyperthermia [19]. Before and after succinyl choline application, lipids were determined in serum and erythrocytes. In one test person it came to a clear increase of the CPK level from the initial 21 U/l to 83 U/l after five weeks treatment, three weeks after the beginning of treatment with 2.4 g/dl of clofibrate. The other test person showed insignificantly increased CPK values. Both test persons felt feeble since the third week of treatment and were clearly handicapped in their activities.

Both test persons showed a slight decrease of the sphingomyelin and lecithin (phosphatidyl choline) content of erythrocytes during the increase in CPK. During succinyl choline induced continuous muscle contraction, an increase of the serum phosphatide level was expected. Olthoff and Kunze [36] showed that primary changes of phosphate content of muscle membrane in progressive muscle dystrophy as well as after the application of myorelaxants become apparent by an increase in the serum lipid level. In the test persons succinyl choline application before clofibrate treatment resulted in an increase in serum phosphatides. After 2.4 g/dl clofibrate for five weeks, however, succinyl choline elicited no increase but even a reduction of some fractions of phosphatide in serum (Fig. 3).

After clofibrate therapy, the EMG after a succinyl choline test showed in patients treated with clofibrate low action potentials in the thenar muscles with shortened duration, further polyphasis with increased frequency. These changes pointed to a drug induced myopathy. After stopping the clofibric acid in the patients as well as in both test persons, a clear rebound phenomenon was observed (Fig. 4); especially the triglyceride fractions were significantly increased (from 137 to 344 mg/dl; from 56 to 170 mg/dl; from 58 to 429 mg/dl).

Discussion

Increased serum levels of CPK and aminoferases found in patients and test persons treated with clofibric

acid, are without doubt signs of a membrane injury of the muscles induced by the drug. In one patient myalgia could be observed, the other patients had no clinical symptoms. The occurrence of a drug induced myopathy was clearly shown by the changed EMG, the changed lipid levels and the positive succinyl choline test. There are several possibilities to explain the phenomenon. Extremely improbable seems to be a direct toxic effect of clofibrate on muscles or an indirect effect by the way of the water balance. More probable is the interpretation based on the effect of clofibrate on lipid metabolism.

In the treatment of hyperlipoproteinaemia with clofibric acid, the only side-effect observed involved the liver, although an effect on muscles which have the ability of cholesterol and triglyceride synthesis may be assumed. The energetic aspect of lipid supply is not supposed to be important.

More essential seems to be an effect on the phosphatide content of the muscle membrane. Unfortunately, the lipid content of the membranes of different cells cannot be compared in absolute values. As a model, erythrocytes come into question, but it is difficult to interpret deviations of erythrocyte lipids [3, 29]. Thus, we interpreted the slight changes in phosphatide concentrations carefully, although they seemed to indicate a membrane effect.

A further interpretation of the myopathic changes is based on the probable correlations between the lipid components of the muscle cell membrane and the serum lipids. Muscle alterations could be seen as a result of a changed serum phosphatide level. The developmental curve of the serum lipid level (Fig. 1) of our first patient (K. E.) would indicate an indirect effect *via* the plasma level. The increase in serum CPK coincided with the greatest decrease per unit of time of phosphatidyl-ethanolamine, sphingomyelin, and phosphatidyl choline. In other patients and in both test persons, no changes of lipid concentration could be observed. The fact that all treated subjects and test persons displayed pathological serum CPK and EMG curves, speaks in favour of the suggestion that the alteration affects not only previously injured muscles [4], but that it is a sign of a drug induced myopathy which affects even the good muscles. The injury of the muscle membrane is thought to be due to changes in serum and lipid synthesis.

Changes of the muscle membrane may occur as a side-effect of anaesthetics and myorelaxants. Especially malignant hyperthermia, a condition probably due to a congenital disturbance of the muscle membrane, has focussed attention to subclinical myopathies as a risk factor of anaesthesia. Today when most anaesthetized patients are treated with clofibric acid or clofibrate, for instance for coronary surgery, the problem is of prime importance.

The hyperlipaemia, especially the hypertriglyceridaemia, observed by

us after stopping clofibric acid treatment, should warn against the discriminate use of clofibric acid, even for the treatment of hyperlipoproteinaemia. Side-effects of clofibric acid have urged us to stop prescribing this drug at our Hospital.

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