Clofibrate-induced myotonia in the rat[1]

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Summary. Clofibrate induced electromyographic and contractile responses in rats consistent with myotonia.

Clofibrate (ethyl-α-p-chlorophenoxyisobutyrate) is used widely in man in the treatment of hyperlipidemia. Although generally well tolerated, recent reports have described a muscle syndrome associated with clofibrate administration characterized by weakness, pain, muscle tenderness, and elevated serum enzymes[2-8]. Apprently, clofibrate has reversible, toxic effects on skeletal muscle which may be dose related. A recent light and electron microscopic examination of muscles from rats injected daily with clofibrate revealed only few abnormal fibres[9]. We have recorded in vivo the electromyographic and contractile responses from rats treated with clofibrate and found them consistent with a diagnosis of myotonia.

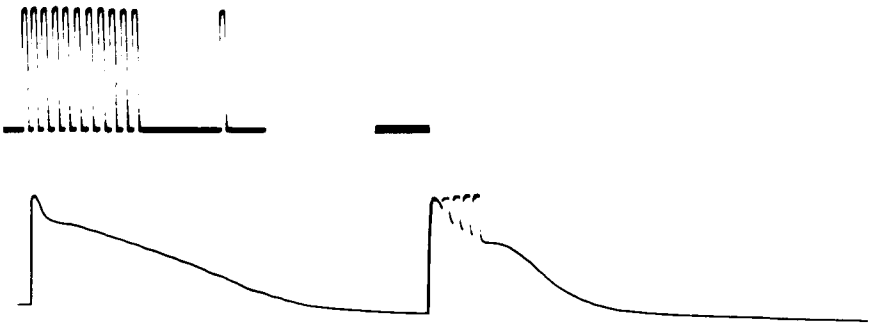
Material and methods. Toxicological doses of clofibrate were administered p.o. or s.c. to male, white Wistar rats approximately 150 g in weight. 1 group of 4 rats was fed ground Purina rat chow (ad libitum) for 3 weeks to which 1% of clofibrate had been added. The drug was dissolved in ether and spread over a thin layer of the diet which was thoroughly mixed to ensure uniform distribution. Each of the 4 other groups (4 rats each) were injected daily s.c. with 1 of the following concentrations of clofibrate: 0.03, 0.3, 0.6 and 0.9 g/kg. The lowest concentration was obtained by diluting the clofibrate with sesame oil and, as control, 4 rats were injected with an equivalent amount of pure sesame oil.

Electromyographic examination of the hind limbs was performed periodically with the animals under light ether anesthesia. Isotonic displacement measurements were performed in vivo with the animals anesthetized with Nembutal. The extensor digitorum longus muscle was exposed on one side, the proximal tendon attached to a displacement transducer lever arm under constant 5-g load and stimulated via embedded flexible wires. Tetanic reponses were recorded by stimulation at 100 Hz for 500 msec.

The concentration of serum cholesterol was determined with the method described by Abell et al.[10]. Analysis for desmosterol was performed by saponification of the serum in alcoholic KOH, and sterol extraction with hexane. The free sterols were separated in a 6-ft glass chromatograph column containing 1% XE-61.

Results. Electromyographic examination of the rats after 2 days of drug administration revealed spontaneous electrical activity and myotonic responses in all the animals except the ones receiving the 0.03 g/kg clofibrate or the pure sesame oil. Needle movement or percussion resulted in a large burst of electrical activity which persisted for several sec. Trains of action potentials which increased and decreased in frequency and amplitude were also recorded. After about a week, the abnormal electrical activity decreased and slowly disappeared even though drug administration was continued.

Isotonic displacement measurements were performed in those rats injected for 4 days with 0.3 and 0.9 g/kg clofibrate. The muscle response for a single stimulus was the same for normal and treated animals. However, tetanic stimulation revealed unusually prolonged relaxation times (figure). Relaxation times ranged from 20 sec to almost 45 sec. Repetitive contraction and relaxation had the effect of reducing the prolonged relaxation time which is characteristic of human myotonia where muscle 'stiffness' may be relieved by exercise. The mean serum cholesterol of rats injected for 6 days (0.6 g/kg) was 67±7 mg/ml; whereas, it was 84±4 mg/ml for untreated animals. Desmosterol could not be detected in either group.



Contractile response to stimulation at 100 Hz for 0.5 sec. Top: normal muscle; bottom: muscle from clofibrate-treated rat. Calibration: 5 sec.

Discussion. The induction of myotonia in rats with steroid inhibitors of cholesterogenesis, such as, 20,25-diazacholesterol has been attributed to the accumulation of desmosterol[11]. The results of this study demonstrate the induction of myotonia in rats without the accumulation of desmosterol. This conforms with the suggestion that clofibrate inhibits the biosynthesis of cholesterol by blocking the production of mevalonate[12], which, in turn, would block the accumulation of desmosterol.

1 This work was supported in part by the Muscular Dystrophy Associations of America. The authors are grateful to Ayerst Laboratories for the generous supply of clofibrate used in this study.

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