Fenofibrate and Human Liver
Lack of Proliferation of Peroxisomes

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Abstract. In rodents fenofibrate shares with other triglyceride-lowering
agents the potential to increase the liver peroxisome population. It was
therefore of interest to look for this effect in hyperlipoproteinemic patients
receiving this drug.

Light and electron microscopy of liver biopsies from a group of 10
patients treated with fenofibrate and from another group of 15 receiving diet
only, show no morphological difference between both groups. In contrast
with the rodent data the morphometric study reveals no significant changes
in the number (fenofibrate group: $7.96 \times 10^{10}$ peroxisomes/cm$^3$; group receiving diet alone:
$8.41 \times 10^{10}$ peroxisomes/cm$^3$ of liver tissue) or in the size (fenofibrate group:
Diameter = $0.53 \pm 0.07$ μm – group receiving diet alone: $0.50 \pm 0.06$) of
peroxisomes.

The difference between our results and those obtained consistently in
rodents may be due to the relatively low dose in man and/or a
species-dependant difference in enzyme content of liver peroxisomes, itself
related to an apparent difference in the way in which lipids are
handled.

Key words: Fenofibrate – Human liver – Electron microscopy –
Morphometry – Peroxisomes

Introduction

Interest in the prevention of cardiovascular diseases has focused the attention of
the medical profession on the detection of primary hyperlipoproteinemias
(HLP) and on the relevance of long-term treatment.

One cause of concern is that, existing drugs such as clofibrate
(ethyl-d-p-chlorophenoxy-isobutyrate) and fenofibrate (isopropyl[4'(p-chloro-
benzoyl)-2-phenoxy-2-methyl[propionate) induce a proliferation of liver peroxisomes in rodents (Barnard et al. 1980; Reddy 1981).

According to Reddy et al. (1980), substances inducing a proliferation and/or an increase in the volume of peroxisomes represent a new class of carcinogenic agents. In fact, if a positive correlation exists in rodents between the proliferation of liver peroxisomes and the development of liver tumours, no cause-and-effect relationship has been established between these two phenomena. Fenofibrate demonstrating a more pronounced hypolipidemic activity compared to clofibrate, is commonly prescribed in long-term treatment in man. It was therefore necessary to study the liver cell state in patients treated with fenofibrate and compare the results with a control group affected by the same metabolic disease but receiving dietary treatment only.

**Material and Methods**

1. **Selection of Patients** (Tables 1 and 2). Twenty-three subjects (mean age 46 ± 11 years; m ± SD age varying between 19 and 70 years) were recruited among patients with hyperlipoproteinemia (HLP) followed at the Department of Metabolic Diseases in the University Hospital Centre of Nancy.

HLP were typed according to WHO criteria (Beaumont et al. 1970). Further tests permitted to exclude secondary HLP (Hypothyroidism, diabetes, nephrotic syndrome, bile obstruction, pancreatitis and dysglobulinemia). The distribution of patients was four type IIa, nine type IIb and ten type IV.

The patients were divided into two groups:

a) **Group 1.** Ten patients (7 δ, 3 Ψ) treated with fenofibrate (2 IIa, 2 IIb, 6 IV).

Five of them received other drug medications (Meprobamate, Equanil, Laboratoires Clin-Midy, Paris, France; Allopurinol, Zyloric, Laboratoires Wellcome S.A., Paris, France; Spironolactone, Aldactone, Laboratoires Searle, Paris, France) unrelated to lipoprotein metabolism and inducing no alterations in peroxisomes (Ghadially 1975; Reddy 1981).

Fenofibrate was given at a daily dose of 300 mg, 400 mg, and 600 mg to 6, 2, and 2 subjects, respectively. The mean duration of treatment was 9.01 ± 7.45 months (m ± SD extreme values: 16 days to 19 months). Among these ten patients, seven received fenofibrate in long-term treatment (duration of treatment ≥ 4 months).

b) **Group 2.** 13 patients (12 δ, 1 Ψ) affected by hyperlipoproteinemia treated by diet only, exclusive of drug medication (2 IIa, 7 IIb, 4 IV).

The two groups were statistically similar from the viewpoint of body-mass index W/H² body weight in kg/height in m, of daily alcohol intake evaluated by dietary enquiry, of the duration of treatment (diet or drug) and of lipid levels when the biopsy procedure was performed.

2. **Techniques for Determining Blood Lipids.** Total cholesterol was determined by the technique of Zlatkis et al. (1953), triacylglycerols (TAG) according to the method of Kessler and Lederer (1965) on Technicon autoanalyser. Lipoprotein electrophoresis was performed on polyacrylamide gel by the technique of Sezille (1976).

3. **Protocol.** The biopsies were obtained with patients' informed consent. The biopsy procedure was performed with local anaesthesia under aseptic conditions. Pre-operative blood coagulation parameters and liver function tests were within normal limits. The liver tissue obtained was chopped into two small portions.