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SHORT COMMUNICATION

EFFECTS OF GEMFIBROZIL TREATMENT ON SERUM LEVELS OF ANDROSTANEDIOL GLUCURONIDE AND ADRENAL ANDROGENS

A. HAUTANEN,[2] M. MÄNTTÄRI,[1] V. MANNINEN,[1] M. H. FRICK[1] and H. ADLERCREUTZ[2]*
[1]First Department of Medicine and [2]Department of Clinical Chemistry, University of Helsinki, Meilahti Hospital, 00290 Helsinki, Finland

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Summary—We have prospectively investigated the role of adrenal cortical androgens as a risk factor for coronary heart disease in the Helsinki Heart Study population. Simultaneously we studied the effects of gemfibrozil treatment on the serum levels of dehydroepiandrosterone (DHEA), its sulfate (DHEAS), and their metabolite androstanediol glucuronide (3αAdiolG) with those of placebo. Gemfibrozil ($n = 133$) vs placebo ($n = 159$) treatment was associated with significant elevation of mean (SD) DHEAS (μmol/l) 8.35 (5.31) vs 6.98 (3.85); $P < 0.02$, and of 3αAdiolG (nmol/l) 17.45 (7.57) vs 8.62 (3.56); $P < 0.001$, and of almost significant elevation of DHEA (nmol/l) 10.12 (6.64) vs 8.78 (5.86); $P < 0.07$. These new observations suggest that gemfibrozil treatment increases the production and turnover of DHEA and DHEAS and may in addition stimulate the 5α-reduction of androgens.

INTRODUCTION

Gemfibrozil (Parke–Davis) is a lipid regulating drug found to induce favorable changes in both plasma low density (LDL)- and high density lipoprotein (HDL)-cholesterol concentrations [1]. Gemfibrozil reduced the incidence of coronary heart disease (CHD) in middle-aged, dyslipidemic men in the Helsinki Heart Study [2]. The primary mode of action of gemfibrozil on lipids and lipoproteins remains unknown, although the most consistent effect seems to be an enhanced activity of lipoprotein lipase [3]. The present work is based on results from a prospective investigation of the role of adrenal cortical androgens as possible risk factors of CHD [4] in the Helsinki Heart Study (HHS) population.

EXPERIMENTAL

The study participants were dyslipidemic (non-HDL-cholesterol > 5.2 mmol/l) middle-aged men, free of CHD at the beginning of the 5 year study. The present study was based on complete data of 292 subjects, 133 on gemfibrozil and 159 on placebo. Frozen sera from the first annual follow-up visit, i.e. 1 year after initiation of the gemfibrozil treatment, were used to determine the hormone levels.

Commercial radioimmunoassay (RIA) kits were used for the determination of dehydroepiandrosterone sulfate (DHEAS) (Wien Laboratories, Inc., Succasunna, NJ, U.S.A.) [intra-assay coefficient of variation (CV) was 6.2% and inter-assay CV 7.5%] and 5α-androstane-3α,17β-diol glucuronide (androstanediol glucuronide, 3αAdiolG) (Diagnostic Systems Laboratories, Inc., Webster, TX, U.S.A.). The intra-assay CV of the 3αAdiolG assay varied between 8.9 and 13.6% (concentration range 1.1–21.8 nmol/l) and the inter-assay CV between 6.0 and 13.7% (range 1.1–24.7 nmol/l). Dehydroepiandrosterone (DHEA) was determined by RIA essentially as described for androstenedione [5] using antiserum from Radioassay Systems Laboratories (CA, U.S.A.). The 25 μl serum sample was diluted with 175 μl buffer and extracted once with 2 ml of petroleum ether (b.p. 40–60°C) and determined by RIA using a final dilution of the antiserum of 1:45,000. Dehydro[1,2,6,7-3H]epiandrosterone (Amersham, code TRK 511) was used as label. The intra- and inter-assay coefficients of variation were 6.3 and 7.7%, respectively.

RESULTS

Subjects treated with gemfibrozil had significantly higher DHEAS, and a tendency to higher levels of DHEA than subjects on placebo. In subjects on gemfibrozil a striking increase of 3αAdiolG concentrations was found (Table 1).

DISCUSSION

The major site of action of fibrates on lipoprotein metabolism has not been discovered with certainly. Our results suggest that gemfibrozil may alter adrenal steroidogenesis by increasing DHEA and DHEAS production. DHEAS is an important precursor of 3αAdiolG, and an increase should lead to elevated 3αAdiolG levels [6 and A. Vermeulen, personal communication]. The very high plasma 3αAdiolG values would suggest that gemfibrozil may, in addition, stimulate the 5α-reduction of androgens. All these observations are new. Among drugs affecting 5α-reduction of androgens may be mentioned MK-906 (Finasteride, Merck Sharp & Dohme) [7], which is a potent inhibitor of the enzyme and significantly lowers the levels of 5αAdiolG in men treated with the drug (own observation). Another drug, Cyclosporine A, shows as a side-effect a significant increase of 3αAdiolG level in plasma [8].

*To whom correspondence should be addressed

Table 1. Mean (SD) values for steroid hormone determinations in gemfibrozil-treated and placebo groups

Steroid	Treatment group		P-value
	Gemfibrozil ($n = 133$)	Placebo ($n = 159$)	
Dehydroepiandrosterone sulfate (μmol/l)	8.35 (5.31)	6.98 (3.85)	0.02
Dehydroepiandrosterone (nmol/l)	10.12 (6.64)	8.78 (5.86)	0.07
Androstanediol glucuronide (nmol/l)	17.45 (7.57)	8.62 (3.56)	0.001

The main source of plasma 3αAdiolG is controversial, but in men it seems to derive mainly from testicular androgens probably mainly testosterone and to a lesser extent from the adrenal DHEAS as opposed to women in which DHEAS is the main precursor [6 and A. Vermeulen, personal communication]. The striking $\approx$100% increase in 3αAdiolG ($P < 0.001$) in the males with dyslipidemia raises the intriguing question, whether serum testosterone levels might also be affected by gemfibrozil treatment. DHEA appears to inhibit glucose-6-phosphate dehydrogenase [9], a key enzyme of the pentose phosphate shunt, which has an important position in the regulation of cholesterol synthesis. Work is therefore in progress to evaluate the levels of other adrenal and testicular steroids to get more insight into the relationship of gemfibrozil treatment with steroid and lipoprotein metabolism.

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