SHORT COMMUNICATION

Effect of phenobarbitone on plasma apolipoprotein B and plasma high-density-lipoprotein cholesterol in normal subjects

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Summary

1. Further observations from an earlier study in which phenobarbitone in a dose of 180 mg daily was administered to ten normal men and women for 3 weeks are reported. There was a significant increase in plasma high-density-lipoprotein (HDL) cholesterol concentration and in the concentration of both total plasma and low-density-lipoprotein (LDL) apolipoprotein B.

2. There was no change in the ratios of the cholesterol : apolipoprotein B and triglyceride : apolipoprotein B in LDL.

3. There was no significant change in plasma very-low-density-lipoprotein (VLDL) apolipoprotein B concentration and the proportion of lipid and apolipoprotein B in VLDL remained unchanged.

4. There was no change in the ratio of HDL : LDL cholesterol concentrations.

Key words: antipyrine clearance, apolipoprotein B, cholesterol, γ-glutamyl transpeptidase, high-density lipoproteins, low-density lipoproteins, microsomal enzyme induction, phenobarbitone, triglycerides, very-low-density lipoproteins.

Introduction

Phenobarbitone has previously been reported to raise concentrations of total serum cholesterol and serum low-density-lipoprotein (LDL) cholesterol in man (Miller & Nestel, 1973; Durrington, Roberts, Jackson, Branch & Hartog, 1976a). Phenytoin, another microsomal enzyme-inducing drug, has also been reported to increase serum cholesterol concentrations (Pelkonen, Fogelholm & Nikkilä, 1975), and more recently to raise serum high-density-lipoprotein (HDL) cholesterol concentrations (Nikkilä, Kaste, Ehnholm & Viikari, 1978). Workers exposed to pesticides have also been found to have raised serum HDL cholesterol (Carlson & Kolmodin-Hedman, 1972). In the present report, samples from an earlier study (Durrington et al., 1976a) were analysed in order to investigate the effects of phenobarbitone on plasma HDL cholesterol. Plasma concentrations of apolipoprotein B were also determined to discover whether the rise in LDL cholesterol, which had previously been observed, was accompanied by a similar rise in apolipoprotein B, which is the principal component of the protein moiety of LDL.

Methods

Seven men and three women took 180 mg of phenobarbitone daily (30 mg twice during the day and 120 mg at bed-time) orally for 3 weeks whilst maintaining their usual diet and alcohol intake. All other drugs were excluded for at least 2 weeks.
before and during the study. No change in body weight was observed.

Total plasma cholesterol and triglycerides, plasma very-low-density lipoprotein (VLDL) cholesterol, triglycerides and protein and LDL cholesterol, triglycerides and protein, antipyrine clearance and serum γ-glutamyl transpeptidase were the subject of an earlier report (Durrington et al., 1976a). The present study concerns concentrations of total plasma apolipoprotein B and plasma VLDL and LDL apolipoprotein B and of plasma HDL cholesterol measured initially and at the end of the period on phenobarbitone.

Apolipoprotein B was measured with a radioimmunoassay employing a monospecific sheep antiserum to human apolipoprotein B (Durrington, Whicher, Warren, Bolton & Hartog, 1976b), which has been shown to be applicable both to whole plasma and to VLDL and LDL (Durrington, Bolton & Hartog, 1978). Plasma HDL cholesterol, determined by subtraction of VLDL and LDL cholesterol from total plasma cholesterol concentration, was subject to considerable variation since it resulted in the summation of the errors in all three estimations. Plasma HDL cholesterol was therefore measured after precipitation of other lipoproteins from 500 μl of plasma by the addition of 50 μl of an aqueous solution of freeze-dried heparin containing 2000 i.u./ml (Boots, Nottingham, U.K.) and 50 μl of manganese chloride solution (0.55 mol/l) (Burstein & Samaille, 1960). Cholesterol was measured enzymatically (CHOD-PAP method; Boehringer Mannheim). Both the apolipoprotein B assay (Durrington et al., 1976b) and the HDL cholesterol method (Miller, Forde, Thelle & Mjm, 1977) have previously been shown to be applicable to frozen plasma. Ten frozen plasma LDL and VLDL samples were available for apolipoprotein B determination and seven were sufficient for HDL cholesterol. Results from before and after the period on phenobarbitone were compared by using Student's t-test.

Results

Total plasma and lipoprotein apolipoprotein B concentrations

There was a statistically significant increase in both total plasma apolipoprotein B concentration from 0.90 ± 0.05 g/l (mean ± SEM) initially to 1.04 ± 0.07 g/l after phenobarbitone and in plasma LDL apolipoprotein B from 0.83 ± 0.06 g/l to 1.00 ± 0.08 g/l (Fig. 1). The concentration of plasma VLDL apolipoprotein B, which did not change significantly, was 0.058 ± 0.005 g/l initially and 0.067 ± 0.006 g/l after phenobarbitone. There was also no change in the ratio of the concentration of cholesterol to apolipoprotein B in LDL or VLDL, nor in the ratio of the concentration of triglycerides to apolipoprotein B in LDL or VLDL.

Plasma HDL cholesterol concentrations

Plasma HDL cholesterol increased significantly on phenobarbitone from an initial mean value of 1.17 ± 0.12 to 1.63 ± 1.20 mmol/l (Fig. 1). The ratio of the concentration of LDL to HDL cholesterol did not change significantly (0.47 ± 0.05 initially and 0.55 ± 0.08 after phenobarbitone). There were no correlations between changes in the concentration of HDL cholesterol and changes in total plasma or VLDL and LDL lipids or apolipoprotein B.

Antipyrine clearance and γ-glutamyl transpeptidase activity

The changes in antipyrine clearance and serum γ-glutamyl transpeptidase previously observed (Dur-
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Durrington et al., 1976a) did not correlate with the changes in total plasma apolipoprotein B or VLDL and LDL apolipoprotein B concentrations or in plasma HDL cholesterol concentration.

Discussion

The increase in plasma and LDL apolipoprotein B concentrations after the administration of phenobarbitone for 3 weeks confirms the earlier observations that phenobarbitone affects LDL metabolism in man (Miller & Nestel, 1973; Durrington et al., 1976a). In the present study, an increase in serum HDL cholesterol was also found. In studies of other drugs known to influence the metabolism of microsomal drug-metabolizing enzymes, such as pesticides (Carlson & Kolmodin-Hedman, 1972) and phenytoin (Nikkilä et al., 1978), increased concentrations of serum HDL cholesterol have been the most striking feature. These studies were, however, in men and women exposed to these substances for long periods of time. The present study and that of Miller & Nestel (1973) were short-term studies and the effects of long-term treatment with phenobarbitone may be different. In the case of alcohol, however, in addition to increased concentrations of serum HDL cholesterol (Johansson & Medhus, 1974; Castelli, Doyle, Gordon, Hames, Hjortland, Hulley, Kagan & Zukel, 1977) there is also evidence for a sustained effect on the metabolism of other lipoproteins (Chait, Mancini, February & Lewis, 1972).

In the present study, the relative proportions of apolipoprotein B and cholesterol in LDL were unchanged by phenobarbitone. There was, however, an increase in the total amount of protein relative to cholesterol in LDL (Durrington et al., 1976a). This suggests that there was an increase in another LDL apolipoprotein, possibly apolipoprotein C. LDL contains two subclasses, LDL₁ (density 1.006–1.019 g/ml) and LDL₂ (density 1.019–1.063 g/ml), of which LDL₁ is believed to be an intermediate in the conversion of LDL₃ into LDL₂ (Eisenberg & Levy, 1975). LDL₂ contains more apolipoprotein C than does LDL₁ and it may be therefore that the increase in total plasma LDL after 3 weeks on phenobarbitone was due principally to a rise in the LDL₁ subclass. Such a conclusion is also supported by the greater increase in LDL triglyceride concentration than that of cholesterol (Durrington et al., 1976a), since LDL₁ is richer in triglycerides than is LDL₂.

There are no precise statistics for the prevalence of ischaemic heart disease in epileptic patients and comparable non-epileptics. However, clinical impression suggests that myocardial infarction is perhaps uncommon in epilepsy (Linden, 1975; Livingston, 1976). For alcohol, evidence suggests that the risk of developing ischaemic heart disease may decrease with increasing consumption (Klatsky, Friedman & Siegelaub, 1974; Stason, Neff, Miettinen & Jick, 1976; Yano, Rhoads & Kagan, 1977). It has been suggested that HDL is protective against ischaemic heart disease (Miller & Miller, 1975) and it may be therefore that the rise in HDL cholesterol with phenobarbitone administration is sufficient to overcome any deleterious rise in LDL. Further study of the effect of enzyme-inducing agents on lipoprotein metabolism may lead to the development of more specific drugs for increasing serum HDL cholesterol.

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References


