SHORT COMMUNICATION

Enzyme induction and serum and lipoprotein lipids: a study of glutethimide in normal subjects

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Summary

1. Serum and lipoprotein cholesterol and triglycerides were measured before, during and after the administration of glutethimide (500 mg daily) for 21 days to six healthy volunteer subjects.
2. Evidence of enzyme induction was provided by significant rises in D-glucaric acid excretion and antipyrine clearance.
4. The time course of these changes was delayed in comparison with the rise and fall in D-glucaric acid excretion.
5. There was no change in the triglyceride content of either whole serum or lipoprotein fractions at any time during the trial.
6. The study provides further evidence that enzyme-inducing agents cause a rise in certain lipid concentrations.

Key words: antipyrine clearance, cholesterol, enzyme induction, D-glucaric acid excretion, glutethimide, lipoproteins, triglycerides.

Abbreviations: VLDL, LDL and HDL, very-low-density lipoproteins, low-density lipoproteins and high-density lipoproteins respectively.

Introduction

Elevated serum lipid concentrations have been reported in patients taking phenobarbitone (Miller & Nestel, 1973) and phenytoin (Pelkonen, Fogelholm & Nikkilä, 1975; Nikkilä, Kaste, Ehnholm & Viikari, 1978) and phenobarbitone administered daily for 3 weeks to normal volunteer subjects caused a rise in low-density- and high-density-lipoprotein cholesterol (Durrington, Roberts, Jackson, Branch & Hartog, 1976; Durrington, 1979). These studies suggested a link between hepatic microsomal enzyme induction and lipid synthesis. The aim of the present study was to investigate the effect of another enzyme-inducing agent, glutethimide (Udall, 1975), on serum lipids and to compare the time course of any changes with the time course of enzyme induction.

Materials and methods

Six healthy non-smokers (four male, two female) aged 20–23 years took part in the trial. They had given their informed consent to participate in the study, which had been approved by the Ethical Committee. They were not taking any medicines and none were heavy drinkers. They were asked to limit their alcohol intake to a maximum of 1 pint of beer per day during the period of the study.

Fasting blood samples were taken on days 1 (control), 2–5, 8, 15 and 22–25. Glutethimide (500 mg) was taken at bedtime on days 1–21.

Serum was fractionated by ultracentrifugation according to the method of Havel, Eder & Bragdon (1955) and analysed for total VLDL-, LDL- and HDL-cholesterol and triglycerides. Cholesterol was estimated by a modification of the Liebermann–Burchard reaction (Robertson & Cramp, 1970) and triglycerides by the standard semi-automated Technicon method (Kessler & Lederer, 1966).
D-Glucaric acid excretion and antipyrine clearance measurements and results have been described elsewhere (Jackson, Homeida & Roberts, 1978).

The statistical significance of changes were analysed by Student's paired t-test.

Results (Fig. 1)

There were significant rises in total serum cholesterol and in VLDL-, LDL- and HDL-cholesterol during the administration of glutethimide in all subjects.

There was no appreciable change in the triglyceride concentrations in either whole serum or lipoprotein fractions.

The rise in total serum cholesterol from baseline (4.80 ± 0.67 mmol/l, mean ± SD), was not significant until day 15 (5.94 ± 1.73 mmol/l, P < 0.05). There was no further change either during medication or in the 3 days after the discontinuation of glutethimide.

Similar changes were found in serum LDL-cholesterol concentrations. The baseline value (2.10 ± 0.46 mmol/l) rose significantly by day 15 (2.78 ± 0.87 mmol/l, P < 0.05). No further change took place, even after the drug was stopped.

Serum HDL-cholesterol showed a significant rise from baseline (1.13 ± 0.08 mmol/l) to day 15 (1.41 ± 0.32 mmol/l, P < 0.05) and similarly remained unchanged until the end of the study.

Serum VLDL-cholesterol showed a more rapid rise from baseline (0.26 ± 0.28 mmol/l) to day 8 (0.43 ± 0.27 mmol/l, P < 0.05). The change was maximum by day 15 (0.70 ± 0.56 mmol/l, P < 0.02) and no further change took place subsequently.

Changes in urinary D-glucaric acid excretion are shown in Fig. 1 (from Jackson et al., 1978). There was a rise within 3 days of starting glutethimide and the values had returned to baseline 5 days after stopping. There was a 55% increase in antipyrine clearance (P < 0.01).

Discussion

We have demonstrated a generalized rise in the cholesterol content of all the lipoprotein classes during the administration of glutethimide, which has been shown to be a potent enzyme-inducing agent as measured by both antipyrine clearance and glucaric acid excretion (Jackson et al., 1978).

The elevations of both total serum cholesterol and the cholesterol content of the lipoprotein fractions was similar to the results of studies with other hepatic enzyme-inducing agents, phenobarbitone (Miller & Nestel, 1973; Durrington et al., 1976; Durrington, 1979) and phenytoin (Pelkonen et al., 1975; Nikkilä et al., 1978). The result is at variance with the studies of Ohnhaus, Kirchhof & Feheim (1979), who found no change in plasma cholesterol after 14 days' treatment with antipyrine, phenobarbitone or rifampicin. Previous reports, however, have not followed the time course of changes in all lipoproteins in response to drug treatment. In the present study a trend was visible within 8 days, but the majority of the changes were not significant until the 15 day blood samples. There was no return to baseline concentrations within a period of 4 days after stopping treatment. This contrasted with the immediate rise and fall in D-glucaric acid excretion at the start and finish of treatment respectively, but is compatible with the reported half-lives of LDL and HDL, but not VLDL (Eisenberg & Levy, 1975). There was no significant change in the triglyceride content of whole serum or lipoprotein fractions. This supports the majority of other reports that triglyceride concentrations are not affected by microsomal enzyme induction, although the findings of Miller & Nestel (1973) and Martin, Martin & Goldberg...
balance of its biosynthesis and catabolism and its distribution between the various sized both in the liver and the intestine (Green, Tall & Wallius, 1978). Since the biosynthesis of salt is also affected by phenobarbitone in rats at the 7α-hydroxylation stage (Shefer, Hauser & Mosbach, 1972). Thus the eventual concentration of serum cholesterol will be dependent on the balance of its biosynthesis and catabolism and its distribution between the various body pools.

Recent evidence suggests that HDL is synthesized both in the liver and the intestine (Green, Tall & Glickman, 1978; Johansson, Rössner & Wallius, 1978). Since the biosynthesis of cholesterol follows the same pathway both in the gut and liver, it is likely that intestinal as well as hepatic enzyme induction occurs. If this is so, then it might account for the finding that HDL-cholesterol concentrations are also elevated during enzyme induction despite their usual inverse relationship with serum VLDL concentrations (Schaefer, Levy, Anderson, Danner, Brewer & Blackwelder, 1978).

The exposure to enzyme-inducing agents, such as drugs, pesticides (Carlson & Kolmodin-Hedman, 1972) or alcohol (Castelli, Doyle, Gordon, Hames, Hjortland, Hulley, Kagan & Zukel, 1977) is widespread and variable. The possible associated effect upon serum lipids might to some extent account for differences in blood lipids between populations, and thereby affect the incidence of atherosclerosis.

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References


