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Lipid-lowering Effects of Two Synthetic Oestrogen Derivatives with Weak Genital Oestrogen Properties

Georg Herbai and Sverker Ljunghall

Department of Internal Medicine, University Hospital, Uppsala, Sweden

ABSTRACT

The effects on serum lipids of two weak synthetic oestrogens were examined in 23 patients, 17 of whom were given cyclofenil and 6 methallenestril for a period of 10 weeks. These compounds have previously been demonstrated to have a much lower effect on the genital organs than on connective tissue compared with natural oestrogens.

With both substances there were during treatment significant reductions of serum triglycerides (mean average reduction 25%) and cholesterol (20%). No side effects were noted.

Previous studies have shown that the net effects of oestrogens on serum lipids depend on their formulation. This study indicates that weak synthetic oestrogens, primarily designed to influence bone and connective tissue, also have lipid-lowering properties which are unrelated to their feminizing capacity.

Key words: Oestrogen, lipids, calcium, hyperparathyroidism

INTRODUCTION

It appears well established that oestrogens affect lipid metabolism. In a large population study (Wallace et al, 1980) menopausal oestrogen treatment was associated with significantly lower levels of LDL (low density lipoproteins) and VLDL (very low density lipoproteins) as well as raised HDL (high density lipoproteins) levels. Hypercholesterolaemia is a common finding in postmenopausal females. Oestrogen administration can reduce both whole serum and LDL-cholesterol (Tikkanen et al, 1979) and a considerable proprotion of oestrogen-treated women will reverse their lipoprotein pattern to their premenopausal configuration (Kay, 1980). In the males can a similar change also be achieved by oestrogens (Barr et al, 1952). It has also been reported that oestrogen treatment reduces the risk for myocardial infarction (Bain et al, 1981; Ross et al, 1981).

All clinical oestrogen use is restricted by the risk of side effects, primarily those related to the influence on the reproductive system. However, the degree of extra-genital effects of different oestrogenic compounds are not dependent on the extent of genital oestrogenicity. Thus, markedly different activities were found in earlier studies comparing genital oestrogenicity and metabolic effects in cartilage of several kinds of oestrogenic substances (Herbai, 1971). In these experiments cyclofenil, a stilboestrol derivative, elicited 500 times stronger inhibition of sulphation than uterotrophic stimulation when compared with equal doses of oestradiol benzoate. Another synthetic derivative, methallenestril, showed a similar type of potency ratio being 50 times more active than the standard oestrogen control.

This dissociation between genital and extra-genital effects made it possible to use these two compounds in clinical trials of progressive systemic sclerosis (Herbai et al, 1977) and primary hyperparathyroidism (HPT) (Herbai & Ljunghall, 1983; 1984). We herein report on their effects on lipid metabolism.

PATIENTS AND METHODS

Altogether 23 patients gave informed consent to participate in the study, 16 were females and 7 males. Their ages ranged from 29 to 74 years with a mean of 62 ± 7 (SD) years. 18 patients (14 females, 4 males) suffered from primary HPT and had a mean serum calcium of 2.77 ± 0.09 mmol/l (range 2.63 - 2.92). Following this study surgery confirmed the diagnosis in all instances. Five patients (2 females, 3 males) with progressive systemic sclerosis were also investigated. All patients had normal values for serum creatinine and liver enzymes.

After routine clinical and laboratory studies treatment was given with either cyclofenil (200 mg 3 times daily, 17 patients) or methallenestril (3 mg twice daily). The effects on serum lipids were evaluated after an average period of 10 weeks. At this time the mean serum calcium in the HPT patients on cyclofenil was 2.62 ± 0.07 mmol/l and in those on methallenestril 2.48 ± 0.05 mmol/l, the reductions with both drugs being highly significant ($p<0.001$) compared with the pre-treatment values.

Whole serum lipids were measured in a Technicon Auto Analyzer II. The normal ranges, based on a local control material are for cholesterol 2.6 - 7.1 mmol/l and for triglycerides 0.23 - 1.70 mmol/l.

Conventional statistical methods were applied and the differences between mean values before and after treatment were calculated by the paired student's t-test.

RESULTS

The results of the ten weeks' course of treatment with the two weak synthetic oestrogens are summarized in Figures 1 and 2. There were significant reductions of the mean values for both serum triglycerides and cholesterol by both compounds. On cyclofenil treatment the reduction of serum triglycerides was from 3.14 ± 2.23 to 2.23 ± 1.27 mmol/l ($p<0.001$) and of cholesterol from 5.56 ± 1.05 to 4.30 ± 0.65 mmol/l ($p<0.001$). The corresponding changes during treatment with methallenestril were a reduction of serum triglycerides from 2.49 ± 0.82 to 1.93 ± 0.56 mmol/l ($p<0.05$) and of serum cholesterol from

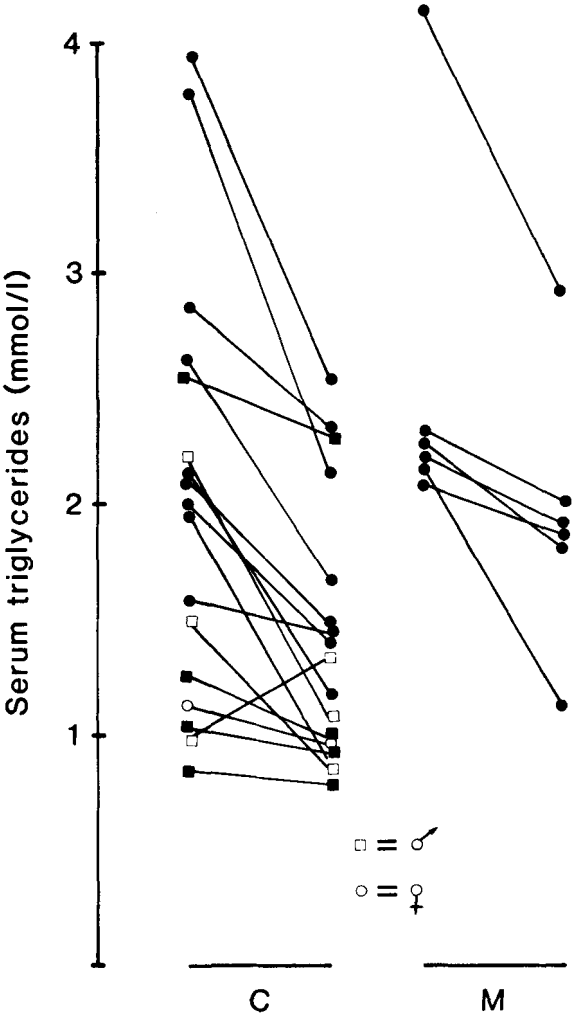

Figure 1. Effects of treatment with cyclofenil (C, left panel) and methallenestril (M, right panel) on whole serum triglycerides in patients with primary hyperparathyroidism (filled symbols) and progressive systemic sclerosis (open symbols).

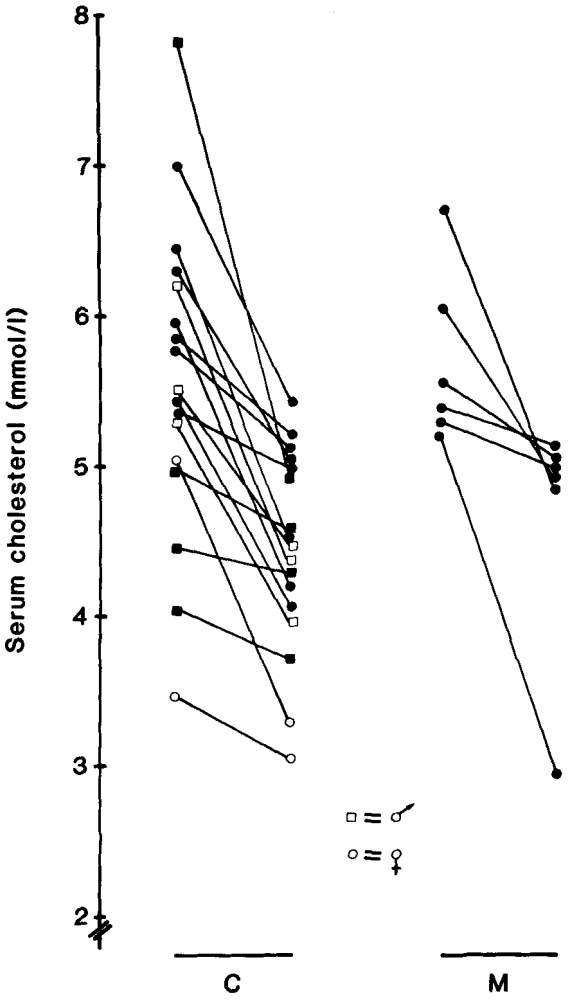

Figure 2. Effects of treatment with cyclofenil and methallenestril on whole serum cholesterol in patients with primary hyperparathyroidism (filled symbols) and progressive systemic sclerosis (open symbols).

5.7 ± 0.6 to 4.6 ± 0.9 mmol/l ($p<0.05$). The greatest reductions were seen in those with the highest pretreatment values.

As can be seen from the figures the responses were similar in males and females as well as when hyperparathyroid and normocalcaemic patients were compared.

DISCUSSION

The net effect of oestrogenic compounds on serum lipids depends on their formulation and various diverging results have been reported from the use of different preparations of oestrogens in postmenopausal women (Wallace et al, 1979; Varma, 1980).

In this study two synthetic, non-steroid, compounds, with low genital oestrogenicity, produced a significant lowering of whole serum lipids. Thus, the lipid-lowering effects appear not to be entirely related to the feminizing properties of the medication.

It cannot be entirely excluded that, at least to some extent, the lipid-lowering action of the synthetic oestrogens could be associated with their action on the underlying disorder for which treatment was given, i.e. primary HPT or progressive systemic sclerosis. Such an explanation is, however, unlikely. It has been earlier reported that when hypercalcaemia in patients with primary HPT is reversed by successful surgery there is an increase of the whole serum levels of both triglycerides and cholesterol (de Moor et al, 1973; Christensson & Einarsson, 1977). These changes have been believed to be the result of a normalization of a catabolic state. In a previous study of HPT patients, where the lipoprotein patterns were investigated both pre- and postoperatively, we found (Ljunghall et al, 1978) that whereas during the first postoperative year there was a reduction of the VLDL triglycerides this was counteracted by an increase of the HDL triglyceride content so that no net changes were discernible in whole serum concentrations. In the same study the surgical normalization of the hyperparathyroid state caused an elevation of the LDL cholesterol as well as the whole serum cholesterol concentrations. Thus, obviously the effects of both cyclofenil and methallenestril, in the present study, on serum lipids cannot be explained as merely secondary to their calcium-lowering capacity in HPT patients. This explanation is further underlined by the observation that the effects on serum lipids were similar in the normocalcaemic patients with progressive systemic sclerosis and in the hypercalcaemic HPT patients.

The present investigation was a pilot study performed to evaluate gross changes of lipid metabolism and was therefore only concerned with whole serum lipids. It is well recognized that significant changes can occur for the different lipoproteins without being detected in whole serum. Further studies might be extended to include lipoprotein analyses.

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