The influence of transdermal oestradiol replacement therapy and medroxyprogesterone acetate on serum lipids and lipoproteins

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Aims The objective of this study was to examine the effects of continuous transdermal oestradiol with or without sequential oral medroxyprogesterone acetate on serum lipids and lipoproteins in menopausal women.

Methods Sixty-two healthy menopausal women, attending at two menopause clinics in Western India, were recruited for this study over a period of 1 year. Group 1 included 38 hysterectomised women being treated with continuous transdermal oestradiol only (50 µg daily). Group 2 included 24 menopausal women with an intact uterus being treated with transdermal oestradiol (50 µg daily) and medroxyprogesterone acetate (10 mg daily for the first 12 days of each calendar month). Women maintained on 50 µg oestradiol throughout 6 months (group 1: $n=22$; group 2: $n=16$) were reviewed for changes in serum lipids and lipoproteins at the end of 6 months (group 1), and between days 8 and 12 of the seventh month (combined phase of treatment) (group 2).

Results In group 1, there was a small reduction in the concentrations of total cholesterol (-5.5% , $P=0.04$) and a small but not significant reduction in LDL-cholesterol (-5.7% , $P=0.16$). In group 2, there were no significant changes in total cholesterol (-4.2% , $P=0.43$) and LDL-cholesterol (-3.9% , $P=0.57$). HDL-cholesterol levels did not change significantly with unopposed transdermal oestradiol ($+3.0\%$, $P=0.53$), or with additional sequential medroxyprogesterone acetate (-3.8% , $P=0.32$). Serum triglyceride concentrations decreased significantly in both the groups (-13.9% , $P=0.01$, and -13.4% , $P=0.008$, respectively). Serum lipid changes did not differ between the groups.

Conclusions Transdermal oestrogen therapy appears to be of particular benefit for women with hypertriglyceridaemia. There were no significant adverse effects of medroxyprogesterone acetate on serum lipids and lipoproteins.

Keywords: transdermal oestrogen therapy, medroxyprogesterone acetate, serum lipids and lipoproteins

Introduction

The beneficial effects of oestrogen replacement upon the risk of arterial disease in menopausal women are mediated through several protective mechanisms. One such mechanism of cardioprotection is related to the favourable influence of oestrogens on lipid metabolism.

For women with an intact uterus, sequential progestagen therapy has been advocated to reduce the risk of endometrial hyperplasia which may be induced by unopposed oestrogen replacement. Progestagens, particularly those with androgenic properties, are believed to oppose some of the beneficial effects of oestrogen on lipid metabolism [1, 2].

This study was undertaken to examine the effects of continuous transdermal oestradiol with or without sequential oral medroxyprogesterone acetate on serum lipids and lipoproteins in menopausal women in Western India, where, the life style, dietary habits and climatic conditions are at variance with those in the western world.

Methods

Sixty-two healthy women, attending at a private menopause clinic and at a menopause clinic in a medical school hospital, were recruited for this study in about 1 year. Group 1 included 38 women who had undergone a hysterectomy and bilateral oophorectomy, and were being treated with transdermal oestradiol only (50 µg per day; Estraderm®, Ciba-Geigy, Basle, Switzerland). Group 2 included 24 perimenopausal ($\text{FSH} > 20 \text{ IU l}^{-1}$) or postmenopausal (amenorrhoea for > 1 year; $\text{FSH} > 20 \text{ IU l}^{-1}$) women requesting relief of menopausal symptoms or requesting replacement therapy for the well-woman effects, and being treated with transdermal oestradiol (50 µg per day; Estraderm) and sequential oral medroxyprogesterone acetate (10 mg per day for the first 12 days of each calendar month; Meprate®, Serum International, Poona, India).

None of the women included in the study were obese, or smokers, or had a known contraindication for hormone replacement therapy (HRT). None had taken HRT during the previous 3 months, or any other medication known to affect lipid metabolism. The women were encouraged to

continue with their normal dietary habits. Informed consent was obtained from the women before the study.

Women maintained on 50 µg oestradiol throughout 6 months were reviewed for changes in serum lipids and lipoproteins. After the women had fasted 12 h overnight, venous blood samples were collected for serum lipids, at baseline, and also at the end of six months in women of group 1, and between days 8 and 12 of the seventh month (oestrogen and progestagen phase) in women of group 2.

Serum total cholesterol and triglycerides were measured by wholly enzymatic procedures (Randox Laboratories Ltd., N. Ireland, and Menarini Diagnostics, Spain, respectively). HDL-cholesterol was measured after precipitation of other lipoproteins with a precipitating reagent (phosphotungstic acid, Mg^{+2}). LDL-cholesterol was calculated using the Friedewald formula [3]. The intra-assay and inter-assay coefficients of variation were less than 5% for all assays.

Baseline and post-treatment values within each group were compared using the paired *t*-test. For comparing the two groups, Student's *t*-tests were used.

Results

After excluding women who withdrew before the end of the study ($n=21$), women who violated the protocol ($n=1$), and women who needed a change in the dose of oestradiol ($n=2$), 38 women who had been maintained on 50 µg oestradiol throughout 6 months were included in the final analysis (group 1: $n=22$; group 2: $n=16$).

The mean ($\pm$ s.d.) age of the women in group 1 was 45.8 (± 7.4) (range 37 to 62) years, and in group 2 46.2 (± 7.5) (range 34 to 60) years.

There were no significant differences in the baseline serum lipid and lipoprotein values between the two groups.

In group 1, there was a small fall in total cholesterol (-5.5% , $P=0.04$) and a small but not significant fall in LDL-cholesterol (-5.7% , $P=0.16$). In group 2, there were no significant changes in total cholesterol (-4.2% , $P=0.43$) and LDL-cholesterol (-3.9% , $P=0.57$). HDL-cholesterol concentrations did not change significantly with unopposed transdermal oestradiol ($+3.0\%$, $P=0.53$), or with additional sequential medroxyprogesterone acetate (-3.8% , $P=0.32$). Serum triglyceride levels decreased significantly in both

the groups (-13.9% , $P=0.01$, and -13.4% , $P=0.008$, respectively) (Table 1).

There were no statistically significant differences in the changes in the respective serum lipids on comparing the two groups ($P>0.3$ for all comparisons, Student's *t*-tests).

Discussion

Transdermal oestradiol has been reported to be less potent than oral oestrogens in obtaining beneficial effects on serum HDL-cholesterol and LDL-cholesterol [4]. The effects of transdermal oestradiol on serum lipids appear to be influenced by the dose and duration of therapy. When used for short-term, serum lipids and lipoproteins remain unaltered [5]. With studies of 6 months or greater duration, the results reported have been inconsistent [6, 7]. The conflicting results may have been influenced by the variable dose and duration of treatment.

In the present study, unopposed transdermal oestradiol induced a fall in total cholesterol while HDL-cholesterol levels remained unaltered. The effects of oestrogen replacement on serum triglycerides depend on the route of administration. While oral oestrogens induce hepatic synthesis of triglycerides resulting in a rise, transdermal oestradiol leads to a fall in triglyceride levels [8]. Our results are in agreement.

Sequential medroxyprogesterone acetate

The effects of oestradiol on serum lipids may be modified by the type, dose and route of administration of the progestagen used to counteract the oestrogen-induced endometrial hyperplasia [9]. Sequential medroxyprogesterone acetate did not exert a significant adverse influence on serum total cholesterol concentrations in our study.

Apart from natural progesterone and dydrogesterone, most progestagens have been reported to oppose the oestrogen-induced rise in HDL-cholesterol [1, 2]. In the present study, sequential medroxyprogesterone acetate had no significant influence on the concentrations of serum HDL-cholesterol. Whitcroft *et al.* have reported a significant reduction in HDL-cholesterol with continuous transdermal oestradiol (50 µg per day) and transdermal norethisterone

Table 1 Effects of replacement therapy on serum lipids and lipoproteins.

	Total cholesterol (mmol l ⁻¹)	HDL - cholesterol (mmol l ⁻¹)	LDL - cholesterol (mmol l ⁻¹)	Triglycerides (mmol l ⁻¹)
<i>Group 1 (n=22)</i>				
Oestradiol only				
Baseline	5.49 $\pm$ 0.94	1.35 $\pm$ 0.23	3.50 $\pm$ 1.00	1.44 $\pm$ 0.65
After 6 months	5.18 $\pm$ 1.08*	1.39 $\pm$ 0.35	3.30 $\pm$ 0.92	1.24 $\pm$ 0.63**
Change (%)	-5.5%	+3.0%	-5.7%	-13.9%
<i>Group 2 (n=16)</i>				
Oestradiol + MPA				
Baseline	5.26 $\pm$ 0.92	1.31 $\pm$ 0.33	3.38 $\pm$ 0.90	1.27 $\pm$ 0.40
After 6 months	5.04 $\pm$ 1.00	1.26 $\pm$ 0.28	3.25 $\pm$ 0.74	1.10 $\pm$ 0.42**
Change (%)	-4.2%	-3.8%	-3.9%	-13.4%

Data are presented as mean $\pm$ s.d. * $P<0.05$; ** $P<0.01$.

acetate (250 µg per day for 14 days per cycle) [8]. In contrast, Erkkola *et al.* reported a significant increase in HDL-cholesterol after 12 months of transdermal oestradiol (50 µg per day) with a low dose of dydrogesterone (10 mg per day for 12 days per month) [10].

Medroxyprogesterone acetate did not significantly alter LDL-cholesterol concentrations. Recent studies suggest a similar lack of reversal of the potentially desirable small fall in LDL-cholesterol induced by transdermal oestrogen, with the use of sequential dydrogesterone and also with sequential transdermal norethisterone acetate [8, 10]. In agreement with other studies [4, 8], our results suggest that progestagens reduce serum triglyceride concentrations.

In conclusion, transdermal oestradiol appears to induce mildly favourable changes in serum lipids and lipoproteins, and may be of particular benefit for women with hypertriglyceridaemia. Although caution must be exercised when making far-reaching conclusions from small numbers of observations, medroxyprogesterone acetate, in a dose of 10 mg per day for 12 days per month, does not appear to attenuate the cardioprotective effects of transdermal oestradiol.

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