ELSEVIER

Maturitas 42 (2002) 157–164

MATURITAS
THE EUROPEAN MENOPAUSE JOURNAL

www.elsevier.com/locate/maturitas

Combined oral estradiol valerate-norethisterone treatment over 3 years in postmenopausal women Effect on lipids, coagulation factors, haematology and biochemistry

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Received 9 July 2001; received in revised form 30 January 2002; accepted 28 February 2002

Abstract

Objective: To determine the effect of continuous estradiol valerate 2 mg and norethisterone 0.7 mg daily as hormone replacement on lipid profiles, coagulation factors, haematology and biochemistry over 3 years. *Methods:* An open label trial with 107–133 postmenopausal women assessed pre-treatment and at annual visits with extensive lipid and coagulation profiles, and observation of circulatory adverse events. Standard haematology and biochemical profiles were also analysed. Results were compared at point of entry and at 36 months. *Results:* Total cholesterol (TC) and HDL and LDL fractions fell significantly ($P = 0.0001$) and there was a significant decline in favourable ratios as well as a rise in VLDL mass ($P = 0.0001$). Lipoprotein (a) (Lp(a)) decreased significantly ($P = 0.0053$). Fibrinogen, free protein, prothrombin time and thrombin increased ($P = 0.0001$) while platelets and KPTT were unchanged. Protein C, antithrombin III and total protein S decreased ($P = 0.0001$) and there was a rise in the frequency of lupus anticoagulant positivity. Significant but small changes were seen in haematology and biochemical parameters although this did not raise safety issues and their clinical significance was uncertain. *Conclusion:* The direction of lipid and coagulation factors move in competing ways, emphasising the complexity of metabolic change and making interpretation of outcome for venous and arterial thrombosis or atherosclerosis difficult to predict. Eight patients developed thromboembolic or ischaemic events over the 3 year period of this study but these patients had lipid changes normally considered beneficial to cardiovascular disease and coagulation changes not thought to be associated with thromboembolism. Decrease in lipoprotein 'a' levels might be an indicator of long-term decreases in atherosclerotic events.

Keywords: Estradiol valerate; Norethisterone; Serum lipids; Coagulation factors; Biochemistry; HRT

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0378-5122/02/$ - see front matter
PII: S0378-5122(02)00039-7

1. Introduction

The importance of establishing lipid and coagulation profiles for each form of hormone replacement has increased since further concerns have been expressed about venous thromboembolic complications during early treatment [1–3] against a decline in arterial events long-term found by some [4] but not all [5,6] studies.

We examined the effect over a 3 year period of treatment with a combination of oestradiol valerate 2 mg (E2V) and norethisterone 0.7 mg (NET) given continuously. We have previously shown that this combination leads to amenorrhoea in the majority of patients, eliminates or markedly alleviates menopausal symptoms, and does not give rise to abnormalities of endometrial histopathology [7]. We also reported that it improved bone mineral density in trabecular bone and prevented bone mineral density loss in compact bone with most patients having a serum oestradiol in a physiological and therapeutic range of 200–350 pmol/l [8].

As part of the trial design, we also studied the effect on lipids, coagulation factors, haematology and biochemistry. We now report the results of these laboratory findings. We have previously detailed the demographic parameters of the study group, the reasons for patient attrition, and the general and serious adverse events over 3 years [7]; we now report specifically on the haematological and biochemical safety parameters and the clinical adverse events related to the cardiovascular system.

2. Methods

In an independent clinical research organisation, a total of 206 postmenopausal women who had not received HRT within the last 3 months and who currently had symptoms requiring therapy were entered and treated in this single centre study. The age range was 41–72. Postmenopause was defined as more than 6 months since the last spontaneous menstrual period. Patients were excluded if they had a current serious medical illness, undiagnosed vaginal bleeding, previous hysterectomy, malignant disease or history of thromboembolism. Concomitant therapy if any was recorded throughout the study.

2.1. Study design

This was an open-label study. Patients acted as their own baseline control and a comparative group was unnecessary since the long duration of the study and the known efficacy of HRT made a placebo study unwarranted. Patients received one tablet a day of E2V 2 mg and NET 0.7 mg continuously. All patients gave written informed consent. The study protocol was approved by the Medical Ethics Committee of the Endocrine Centre and ethical approval was obtained for each year of the study.

2.2. Assessments

Blood sampling for lipids, coagulation factors, routine haematology and biochemistry (following a 12 h fast) were determined at the initial pre-treatment visit and annually. At the pre-treatment clinical visit the patient was asked for symptoms in addition to menopausal and at each subsequent visit any adverse event was elicited by direct questioning. The assays were undertaken using standard methodology by Omnilabs Clinical Pathology, 27 Harley Street, London W1N 1DA, a clinically accredited laboratory. Identical procedures were used throughout the 3 year period of the study and data on methodology, procedure and quality control are available on request.

2.3. Statistical analysis

An analysis policy was determined before the start of the study, and for all the laboratory parameters was on a per protocol patient, the reason for which includes the fact that an intention-to-treat policy would not permit analysis of uniformly paired data. For evaluation of changes versus baseline, both paired t-tests and the Wilcoxon matched-paired signed-ranks tests were applied; usage of both these tests allows the test with the lower (stricter) P value to be chosen if results are different. Both t-tests and the

Table 1
Effect of oestradiol valerate/norethisterone on mean (S.D.) serum lipid levels over 3 years

	TC	HDL	HDL_2	HDL_3	LDL	VLDL	Triglyceride	TC/HDL	LDL/HDL	Apo A	Apo B	Lipo (a)
Pre-treatment	6.78 (1.19)	1.71 (0.39)	0.40 (0.17)	1.33 (0.28)	4.48 (1.08)	0.45 (0.29)	1.25 (0.60)	4.18 (1.21)	2.79 (1.04)	1.99 (0.34)	0.99 (0.96)	0.28 (0.26)
Year 1	5.79 (0.97)	1.42 (0.31)	0.31 (0.11)	1.10 (0.21)	3.83 (0.88)	0.40 (0.27)	1.18 (0.63)	4.26 (1.18)	2.85 (0.99)	1.78 (0.25)	0.78 (0.17)	0.19 (0.20)
Year 2	5.81 (0.92)	1.40 (0.29)	0.24 (0.09)	1.16 (0.22)	3.88 (0.87)	0.50 (0.38)	1.18 (0.63)	4.33 (1.22)	2.92 (1.06)	1.72 (0.25)	0.95 (0.20)	0.25 (0.32)
Year 3	5.75 (0.96)	1.40 (0.29)	0.37 (0.14)	1.01 (0.19)	3.80 (0.87)	0.59 (0.46)	1.20 (0.64)	4.27 (1.17)	2.85 (1.00)	1.54 (0.27)	1.15 (0.30)	0.20 (0.26)
Stats P (t)	<0.0001	<0.0001	0.003	<0.0001	<0.0001	<0.0001	0.996	0.0009	0.0096	<0.0001	0.0009	0.0096
Stats P (w)	0.0001	0.0001	<0.0001	0.0001	0.0001	<0.0001	0.519	0.0002	0.0053	0.0001	0.0003	0.0053
n	133	133	109	109	133	132	133	133	133	109	109	109

Lipid values for TC, HDL, HDL_2, HDL_3, LDL, VLDL and triglycerides are mmol/l; apolipoprotein A1, apolipoprotein B and Lp(a) are g/l. Ratios (TC/HDL, LDL/HDL) were individually calculated and then meaned. Statistical significance compares paired data of pre-treatment with 3 Year values; n is number at 3 years.

Wilcoxon tests were computed by the Stata Statistical System (version 5.0, Computing Resource Centre, Texas).

3. Results

Two hundred and six patients entered the study, 42 did not complete year 1, a further 20 did not complete year 2 and 11 did not complete year 3. At the end of year 3 there were 133 evaluable patients (at least 107 for some factors). The reasons for non-completion have been described in a previous report [7] and included adverse effects, failure of compliance, not wishing to continue with HRT and patient non-attendance. It was not possible to obtain specimens for laboratory testing on patients who dropped out and did not re-attend the clinic, and the per protocol patient analysis policy required paired data.

3.1. Lipids

Lipid profiles are shown in Table 1 for each year of study. The statistical data compares baseline with 3 years results. There were significant falls in total cholesterol (TC), HDL, HDL_2 and HDL_3, LDL, apolipoprotein AI and lipoprotein (a) (Lp(a)). There was no change in triglyceride levels. There were significant rises in VLDL mass, TC–HDL ratio, LDL–HDL ratio and apolipoprotein B.

3.2. Coagulation factors

The paired data at baseline and the end of 3 years are shown in Table 2 with 107 patients giving comparable data (platelets, $n = 132$). There were no significant changes in platelets or KPTT. Significant increases occurred in fibrinogen, free protein, prothrombin time and thrombin levels. Significant declines were seen with protein C, antithrombin III, and total protein S.

Lupus anticoagulant prior to treatment was negative in 115 of 119 samples, equivocal in two and positive in two; at the end of 3 years it was negative in 92 samples, equivocal in four, and positive in 11. Only one of these patients had a significantly raised anticardiolipin antibody titre.

Table 2
Paired mean (S.D.) coagulation data at baseline and end of 3 year ($n = 107$)

	Pre-treatment	Year 3	P (t)
Platelets	260 (52.8)	258 (54)	0.63
Fibrinogen	3.42 (0.69)	4.05 (0.83)	<0.0001
Protein C	1.44 (0.30)	1.05 (0.22)	<0.0001
Anti-thrombin III	1.15 (0.14)	0.99 (0.16)	<0.0001
Total protein S	1.28 (0.34)	1.05 (0.19)	<0.0001
Free protein	0.36 (0.16)	0.45 (0.11)	<0.0001
Prothrombin time	12.2 (0.70)	12.53 (0.94)	<0.0001
KPTT	32.3 (3.6)	31.9 (3.3)	<0.13
Thrombin	14.7 (1.1)	16.0 (1.4)	<0.0001

Platelets $\times 10^9$ per l, fibrinogen in g/l, protein C and antithrombin III in IU/ml, total protein S and free protein in μg/ml, and prothrombin time, KPTT and thrombin in seconds.

3.3. Haematology and biochemistry

At the end of 3 years there were 133 patients with paired values (Tables 3 and 4). Small but significant changes in a number of parameters were seen and are recorded for safety reasons.

3.4. Adverse events

Circulatory adverse events, together with relevant lipid and coagulation data for individual patients, are recorded in Table 5. Five adverse

Table 3
Paired mean (S.D.) haematological values at baseline and end of 3 year ($n = 133$)

	Pre-treatment	Year 3	P (t)
Haemoglobin	13.62 (1.40)	13.65 (0.94)	NS
RBC	4.60 (0.35)	4.48 (0.34)	<0.0001
HCT	0.41 (0.03)	0.41 (0.03)	NS
MCV	89.6 (4.7)	91.6 (5.4)	<0.0001
MCH	29.9 (1.5)	30.57 (1.9)	<0.0001
MCHC	33.4 (1.2)	33.4 (0.8)	NS
WCC	5.91 (1.59)	6.75 (1.66)	<0.0001

Haemoglobin in g/dl, RBC (red blood cells) $\times 10^{12}$ per l, MCV in fl, MCH in pg, MCHC in g/dl, and WCC (white cell count) 10^9 per l.

Table 4
Paired mean (S.D.) biochemical values at pre-treatment and end of 3 year ($n = 133$)

	Pre-treatment	Year 3	P (t)
Sodium	141 (2.1)	140 (2.2)	NS
Potassium	4.06 (0.48)	4.12 (0.29)	NS
Urea	5.26 (1.24)	4.69 (1.18)	<0.0001
Creatinine	81.6 (11.7)	85.1 (10.2)	<0.0001
Glucose	4.9 (0.5)	4.7 (0.5)	<0.0001
Bilirubin	10.5 (4.8)	11.0 (4.8)	<0.0001
Alanine transferase	23.4 (14.3)	18.9 (12.7)	<0.0001
Aspartate transferase	24.1 (9.6)	19.8 (7.3)	<0.0001
γ glutamyl transferase	23.2 (20.5)	24.3 (23.4)	NS
Total protein	73.0 (4.3)	72.3 (4.4)	<0.0001
Albumin	46.9 (2.8)	44.7 (2.5)	<0.0001
Globulin	26.5 (3.8)	27.7 (3.2)	<0.0001

Sodium, potassium, urea, glucose and aspartase transferase in mmol/l; creatinine and bilirubin in mmol/l; alanine transferase and γ glutamyl transferase in IU/l; total protein, albumin and globulin in g/l.

circulatory events occurred in the first year, two in the second and one in the third. Total cholesterol (TC) levels decreased during the study period for all seven patients for whom data are available; TC/HDL ratios fell in four and rose in three, and the mean for the seven patients decreased from 4.38 to 4.16. Apolipoprotein AI increased in one and decreased in six; lipoprotein(a) was unchanged in four and fell in two.

Coagulation factors for the six patients for whom data are available showed fibrinogen increased in two patients and decreased in four; anti-thrombin III rose in one, fell in four, and was almost unaltered in one; whilst KPTT increased in two and decreased in four.

4. Discussion

Changes in lipid profiles were variable, with a contradictory mixture of parameters normally considered to be favourable or unfavourable to circulatory disease. Thus there were statistically significant falls in mean TC and apolipoprotein A, but a significant decrease in mean HDL and a (small but) significant increase in TC/HDL ratios. At the same time there were significant falls in mean LDL and in mean Lp(a). The latter has aroused considerable interest in recent years because the apoprotein 'a' component of the molecule is an independent risk factor for coronary artery disease [9]. The LDL properties of Lp(a) may also confer atherogenic potential and this links the two systems most implicated in thrombotic and atherosclerotic disease. Significant falls in Lp(a) have been shown in other studies with oral oestradiol alone [9] or in combined HRT [10], an effect which we confirm, these 3-year data being of particular interest since HRT is one of the very few physiological or pharmacological substances which influences the level of Lp(a). This long term effect in particular could account for a favourable outcome on atherogenic events.

For individual patients with circulatory adverse events (see Table 5), the lipid changes for the majority appeared to be in a direction normally considered beneficial (falls in TC, LDL, TC/HDL ratios) and on a clinical basis should have been helpful in preventing such events. Lp(a) decreased in two of the six patients for whom data were available, and were essentially unchanged in four.

There were variable outcomes also for coagulation factors, with significant increases in mean fibrinogen and thrombin levels together with decreases in anti-thrombin III levels, but significant increases in prothrombin times, whilst mean platelets and KPTT showed no significant change. However, the majority of patients with circulatory adverse events had changes usually thought not to be associated with thromboembolic phenomena (Table 5).

Coagulation factors results from other studies with the same or different oestrogens and progestogens have shown either no change in platelet counts [11,12], no change [11–15] or decreases in fibrinogen levels [16–18], generally decreases [16–19] or no change [13,20] with anti-thrombin III, generally increases [13,15,16] or no change [14,20] with plasminogen, decreases of plasminogen activator inhibitor I [14,17,20], variable changes with protein C or free protein [13,16] and contradictory [15,17] or no change [11] with Factor V.

Venous thrombotic risk was increased by HRT with oestrogen alone or with oestrogen–progesterone [1–3]. One mechanism is thought to be through a mutation of one of the proteins (Factor V Leiden) involved in the coagulation cascade [21]. The risk of thromboembolism is enhanced more than 30-fold in women who have Factor V Leiden mutation and take oral contraceptives [22]. If the same applies to HRT-takers, then clearly sub-groups of highly at risk patients may strongly influence the incidence of venous thromboembolism; screening would exclude this group and allow greater use of HRT in the majority of patients for whom there is little risk but important

Table 5
Circulatory adverse events over 3 years and selected lipid and coagulation data

	Pt number	Adverse effect	Lipid data	Coagulation data	Comment
Year 1	77	Phlebitis	TC 8.20→7.28 HDL 1.87→1.68 LDL 5.30→5.04 ApoA 2.02→2.16 Lp'a' 0.05→0.05	Fibr 3.42→3.60 A-T III 1.24→1.50 KPTT 30.6→26.2	A-T III raised pre-Rx. Continued into year 2
	83	Phlebitis	TC 9.50→7.37 HDL 2.06→1.46 LDL 7.03→5.30 ApoA 2.08→1.92 Lp'a' 0.80→0.06	Fibr 4.04→3.73 A-T III 1.15→0.99 KPTT 30.9→25.5	Onset 5 months into study. Fibr raised pre-Rx. Continued into year 2
	95	DVT	TC 7.26→5.53 HDL 2.36→1.57 LDL 4.54→3.59 ApoA 2.04→1.76 Lp'a' 0.51→0.15	Fibr 2.90→2.32 A-T III 1.14→1.01 KPTT 32.5→28.7	DVT followed clavicle fracture. Possible previous DVT pre-Rx. Continued into year 2
	140	Phlebitis	TC 80.8→6.07 HDL 2.01→1.79 LDL 5.52→3.84 ApoA 2.29→2.21 Lp'a' 0.21→0.23	Fibr 3.89→3.42 A-T III 1.15→1.13 KPTT 33.3→27.6	Onset 4 months into study. No complaints at later visits. Continued into year 2
	188	DVT	No paired data	No paired data	DVT occurred post-operatively. Withdrawn as precaution
Year 2	14	Angina	TC 6.75→5.33 HDL 1.70→1.52 LDL 4.57→3.62 ApoA 2.13→1.68 Lp'a' 0.93→0.90	Fibr 4.02→4.62 A-T III 1.23→1.00 KPTT 32.7→34.1	Two episodes angina. Onset 13 months into study.
	48	SVT	TC 8.10→5.87 HDL 1.19→1.11 LDL 6.00→3.84 ApoA 1.85→1.75 Lp'a' 0.05→0.05	Fibr 5.07→3.73 A-T III 1.35→1.08 KPTT 28.3→30.1	SVT after ankle fracture. Withdrawn (lab data = end Year 1)
Year 3	237	Chest discomfort	TC 6.10→4.15 HDL 1.60→1.00 LDL 4.10→2.55 ApoA no data Lp'a' no data	No data	Coronary angiogram showed triple vessel disease. Continued on Rx.

Paired values refer to results at baseline and year-end of adverse effect. DVT, deep vein thrombosis. SVT, superficial venous thrombosis. Rx-treatment. All cholesterols in mmol/l. TC = total cholesterol. ApoA = apoliprotein A (g/l). Lp'a' = liproprotein 'a' (g/l). Fibr = fibrinogen (g/l). A-T III = anti-thrombin III (IU/l). KPTT in seconds.

benefits. Screening for at-risk sub-groups will be of growing importance.

We did not screen for Factor V Leiden or Factor II and the results of factors for which we did screen would not have led us to exclude any patient from entry to the study. The venous thrombotic episodes that were observed in this group could not have been predicted from our profiles. Two which occurred in the first year might or might not have been due to preceding events.

Lupus anticoagulability tests showed an increase in the number of positives, from two pretreatment to ten at the end of 3 year. Some published studies have reported significantly increased relative risks of developing systemic lupus erythematosus (SLE) in women taking HRT for 2 years or more [23,24], but others have found no difference in women with established SLE between HRT-takers and non-takers in the rate or magnitude of flares [25,26]. We did not see any clinical evidence of systemic or discoid LE.

The haematology and biochemistry safety investigations showed a number of small but significant changes whose clinical importance is unclear. The significant decline in serum albumin and increase in globulin with a decrease in total protein is probably related to the well-established oestrogen hepatic effect on protein production. Alteration in serum proteins might influence the level of certain serum lipids and coagulation factors. Fasting glucose levels were (statistically significantly, but minimally) lower suggesting improved glucose tolerance, but insulin-glucose responses have given contradictory findings [19].

In conclusion, we observed that this combination of E2V 2 mg and NET 0.7 mg given daily and continuously over 3 years gave rise to lipid changes both favourable and unfavourable to circulatory disease, led to significant changes in coagulation factors which taken as a whole might suggest hypercoagulability and were associated with adverse events in the circulation in a small number of patients whose lipid and coagulation changes during treatment were not thought to be associated with thromboembolic phenomena. It may be that identification of abnormal coagulation proteins such as Factor V Leiden or Factor II will enable the benefits of hormone replacement to be more safely delivered but our lipid and coagulation screening, although extensive, was not helpful in predicting circulatory event outcome. The important benefits of relief of symptoms, well-being, amenorrhoea and improved bone mineral density, previously reported [7,8] should not be neglected.

Acknowledgements

We would like to thank Professor K.D. MacRae, Professor of Medical Statistics, European Institute of Health and Medical Sciences, University of Surrey, Guildford, for his help with all the statistical analyses. Funding: The clinical study was supported by various pharmaceutical companies. The product is now distributed as Climesse® and Merigest®.

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