A randomized comparative study for the clinical evaluation of hormone replacement by transdermal and oral routes

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Summary: During a six-month randomized study involving 460 post-menopausal women, transdermal estradiol has proved to be as effective as oral conjugated equine estrogens in the control of menopausal symptoms and to produce similar estrogenic effects on the endometrium.

The group of patients treated with transdermal estradiol showed better compliance and had fewer drop-outs. Moreover, the quality and duration of menstrual bleeding were considered more physiological in the transdermal estradiol group than in the orally treated patients.

The trial was carried out with the co-operation of 17 Italian University Centres, under the supervision of Ciba-Geigy Italy S.p.A. Medical Department.

Key words: Post menopause; Transdermal replacement therapy.

INTRODUCTION

The benefits of estrogen replacement therapy in postmenopausal women have been clearly demonstrated. The reduction of somatic and psychological symptoms and the prevention of long-term metabolic disorders, such as osteoporosis and cardiovascular disease is well known among treated patients.

For all these reasons, estrogen replacement therapy is now widely accepted as the most appropriate treatment for the climacteric syndrome; but, as there is still much uncertainty regarding the risk/benefit ratio, it is essential to provide the most effective treatment with the fewest side effects. In fact, it is also well known that the metabolic effects of estrogen vary considerably according to the route of administration.

Oral estrogens are the most common form as replacement therapy, but not necessarily the best.

Unlike parenteral estrogens, such as transdermal estradiol, orally administered estrogens are absorbed through the gut wall and enter the liver. This is fundamentally important, because the passage of estrogens through the liver leads to certain effects which do not occur with parenteral administration. The liver is extremely sensitive to estrogen and oral therapy increases the serum concentration of a number of proteins. While not all of these changes should be regarded as being adverse, the well known increase in protein (such as renin substrate and coagulation factors) during oral therapy may be related to the risk of hypertension and venous thromboembolism.

Crane *et al.* (1971) pointed out that some postmenopausal women taking oral conjugated equine estrogens developed

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severe hypertension while on therapy. They showed that these subjects had a imbalance of the renin-angiotensin system and that withdrawal of estrogens resulted in a return to normal blood pressure and a reversal of the abnormal renin-angiotensin levels.

As far as the association with thromboembolic disease is concerned, the oral contraceptive pill is known to increase the risk of thromboembolism in young women by increasing platelets aggregation and production of clotting factor by the liver, as some studies report; however, the major studies reporting the risks of hormonal replacement therapy have failed to show any increase in the incidence of this phenomenon.

On the other hand, estrogens are thought to protect against atherosclerosis and cardiovascular disease by increasing the high density/low density lipoprotein ratio. Both oral and parenteral estrogens have been shown to reduce LDL cholesterol, but only oral estrogens have been shown to increase HDL. For this reason, oral replacement might have a better effect on lipid metabolism than parentereal therapy but, as yet, there are no studies showing a difference in the incidence of ischaemic myocardial disease.

Another problem arising from the use of oral replacement therapy is the plasma levels of estradiol/estrone ratio. In fertile and premenopausal women there is a very high ratio; in postmenopausal women, when there is no natural release of estrogens by the ovary, the estradiol/estrone ratio is reduced. When estradiol is orally administered, much of it is converted to estrone by oxidation, so that the ratio of estradiol to estrone is reversed (Jacobs *et al.*, 1977).

On the contrary, this does not occur in women treated with parenteral estradiol, which is absorbed as such and only partially converted to estrone as a results of its normal metabolism.

MATERIAL AND METHODS

This study was carried out by 17 Centres located throughout Italy. The purpose of the study was to compare the efficacy and tolerability of estradiol administered by transdermal route, with oral estrogens in the treatment of postmenopausal symptomatic women.

Four hundred and sixty women (mean age 49.7 years) were selected for the study: all of these patients were postmenopausal and only one had been subjected to surgical menopause. The elapsed time since the last menstrual bleeding had been from 1 to 4 years. The transdermal therapeutic system, releasing 50 mcg of estradiol daily was administered according to a three weeks cycle, with one week hormone free.

This treatment was randomly compared with that of the oncedaily administration of tablets containing conjugated equine estrogens 0.625 mg for three weeks per cycle. In both cases, estrogens were used in combination with medroxyprogesterone acetate (MPA) given orally at a dose of 10 mg/day during the last 12 days of every cycle.

Kupperman's index was used to evaluate the efficacy of the two therapeutic regimens in the control of postmenopausal symptoms. Analysis of variance was used to compare pre-study values with those at two, four and six months.

Endometrial biopsy, by the VABRA suction method, was taken before the study and repeated after six months of treatment; vaginal cytology and gynaecological examinations were performed at the same times.

In order to evaluate the tolerability and metabolic changes of the different replacement the-

Table 1. – *Multicentre italian study results.*

- Recruited patients: 460.
- Patients at the end of the study: 373 (81%).
  - Transdermal estradiol: 242/203 (84%).
  - Oral cee: 218/170 (78%).
- Causes of premature discontinuation of therapy:

	Transdermal	Oral
Side-effects	16 (6.6%)	15 (6.9%)
Worsening of pre-existing disease	1 (0.4%)	5 (2.3%)
Causes not depending on therapy	9 (3.7%)	4 (1.8%)
Unknown causes	4 (1.7%)	4 (1.8%)
Low compliance	9 (3.7%)	20 (9.2%)
Total	39	48

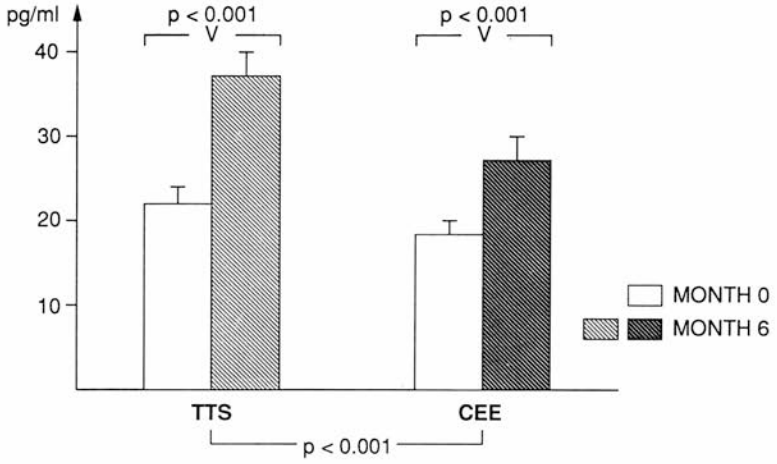

Fig. 1. — 17-β-estradiol (7 centres/130 patient).

rapies, a series of blood and urinary tests was performed before and at the end of the study: routine haematologic, hepatic and renal screenings, clotting factors (fibrinogen, antithrombin III, PT and PTT), lipids (total cholesterol , LDL, HDL and triglycerides) and calcium metabolism (plasma calcium and phosphorus levels, alkaline phosphatase, urinary excretion of calcium, phosphorus and hydroxyproline, urinary creatinine).

Hormone levels (estradiol, estrone, progesterone, prolactin, FSH and LH) were measured in order to evaluate any difference between the two treatments. Clinical parameters, such as weight, height, blood pressure and pulse rate were also recorded.

RESULTS

In a multicentre study, problems arise at the moment of data evaluation. The fact that the laboratory tests are not centralized requires some particular statisti-

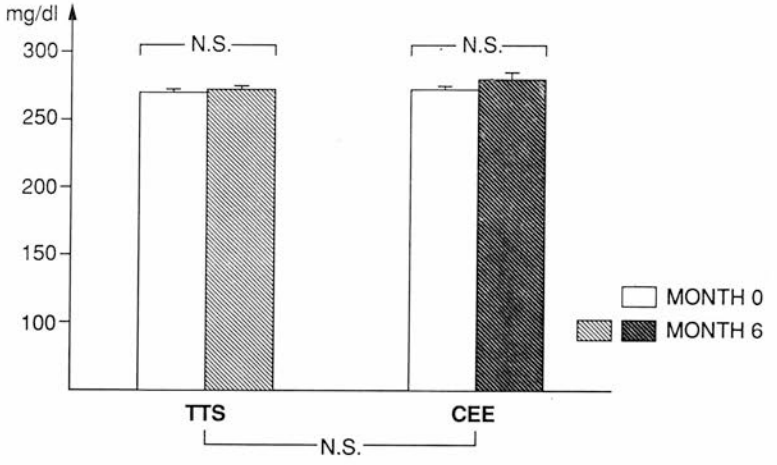

Fig. 2. — Fibrinogen (12 centres/302 patients).

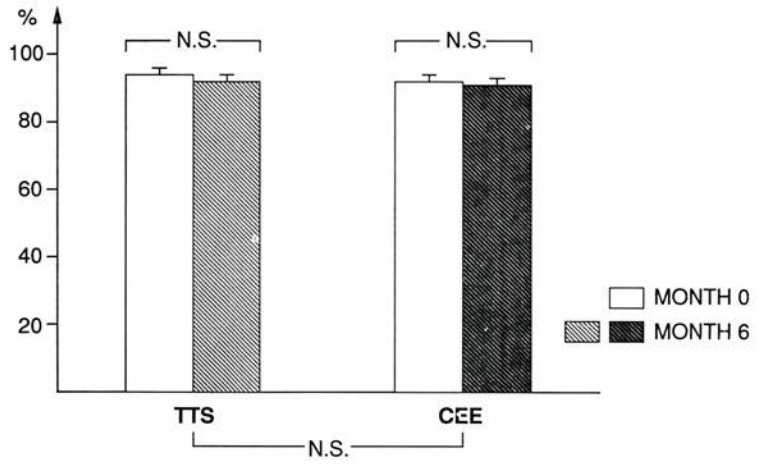

Fig. 3. — Antithrombin III (9 centres/198 pazients).

cal elaboration, but subjective results, such as tolerability and compliance, are indisputable.

Tolerability and compliance

At the end of the six-month study, 87 patients had discontinued their therapy prematurely. 39 from the transdermal group and 48 from the oral group. A total of 373 patients (81%) was included in the analysis. The causes of drop-out are shown in Table 1. It is clear that compliance was better in the transdermal than in the oral group, whereas side-effects were the same for both treatments.

Metabolic effect

The transdermal route is known to protect the liver from the excessive amounts of estrogen absorbed when oral estrogen

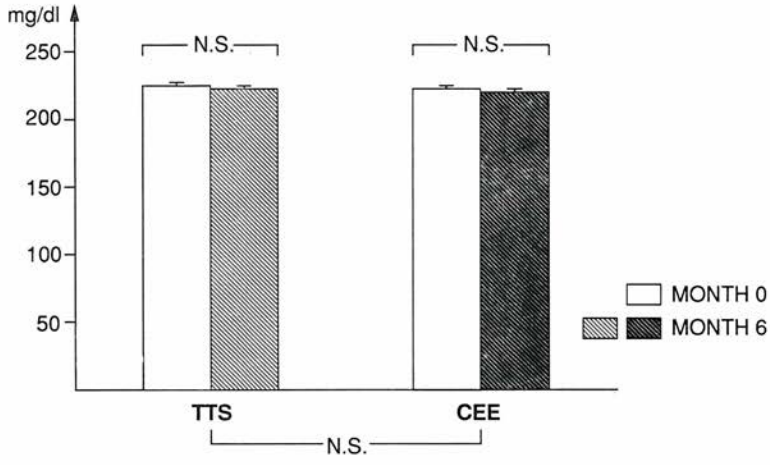

Fig. 4. — Total cholesterol (13 centres/338 patients).

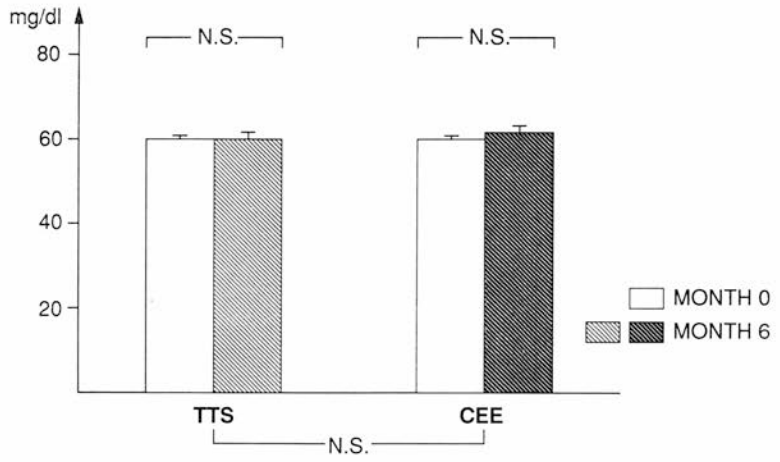

Fig. 5. — HDL-cholesterol (8 centres/206 patients).

preparations are used. In addition, this administration route assures that a constantly low rate of estradiol passes directly into the blood circulation. In this study, serum concentrations of estradiol during therapy were closer to the physiological follicular phase in the transdermal group than in the orally treated patients (Fig. 1).

At the end of this study, no alterations in the results of haematologic, hepatic and renal tests were found. Nor were there any significant differences in clotting factors between the two groups (Fig. 2, 3).

As far as lipid patterns are concerned, both oral and parenteral estrogens decreased total and LDL cholesterol, although not in a statistically significant way. No variation in HDL cholesterol or triglycerides was found (Fig. 4, 5, 6, 7).

With a six month study it is impossible to evaluate the efficacy of any treatment

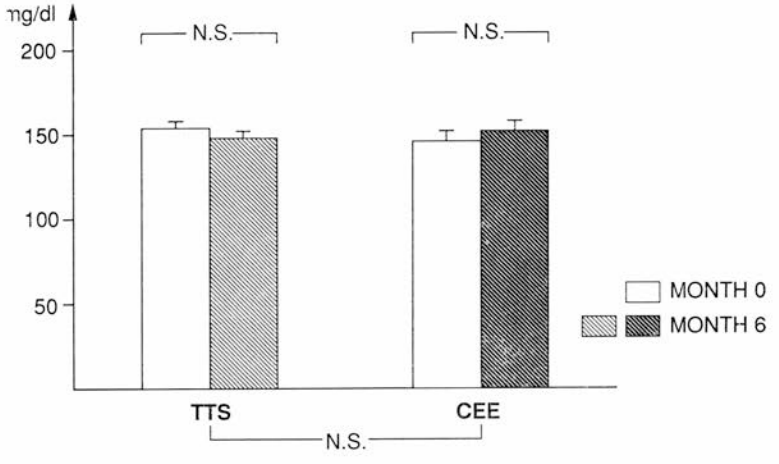

Fig. 6. — LDL-cholesterol (8 centres/141 patients).

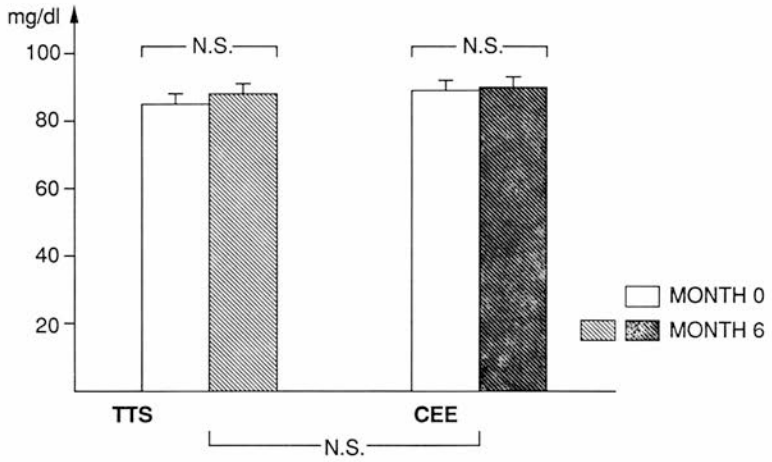

Fig. 7. — Triglycerides (10 centres/217 patients).

in terms of bone loss prevention. However, both estrogen preparation lowered both urinary calcium and hydroxiproline excretion.

As Table 2 shows, no significant levels variations were found in weight and blood pressure.

Efficacy

To evaluate subjective parameters, such as symptoms, Kupperman's index is nowadays the most widely used. In this study, the analysis of variance of Kupperman's index showed that both treatments were similarly effective. Overall, symptoms such as hot flushes and sweating, anxiety, loss of memory, vaginal drynes and sexual disturbances were well controlled in both groups. The results of the statistical analysis are shown in Table 2.

Bleeding and endometrial response

Estrogen replacement therapy in women with an intact uterus requires the cyclical addition of a progestin to protect the endometrium from the possible neoplastic effects of unopposed estrogens. The progestin used in this study was Medroxyprogesterone acetate, which has had very few undesirable effects on hepatic function.

Table 2. – *Multicentre italian study results.*

	Transdermal		Oral	
	Month 0	Month 6	Month 0	Month 6
Weight (kg)	60.9± 8.5	61.6± 8.6	60.8± 7.6	61.5± 7.6
SBP (1) (mm/Hg)	124.2±15.3	124.6±13.8	126.3±11.8	125.7±10.7
DBP (2) (mm/Hg)	79.6± 9.3	80.0± 8.9	80.8± 8.5	80.3± 7.3
Kupperman's index	24.9± 9.0	52.± 5.0 (3)	24.7± 8.6	4.8± 4.1 (3)

– Clinical parameters. – Kupperman's index.
(1) SBP = Systolic arterial pressure (2) DBP = Diastolic arterial pressure (3) $p<0.0001$ vs Month 0

In the opinion of the physicians involved, the quality and duration of menstrual bleedings were considered more physiological in the transdermal group that in orally treated patients. The reason is that the serum concentrations of orally administered estrogens is higher and persists longer than those of transdermally administered estrogens.

Endometrial response was analysed at the end of the study. Both therapies produced similar estrogenic effects on the endometrium, with only 4 cases of hyperplasia in each group of patients (2% in the transdermal and 2.3% in the oral group).

CONCLUSIONS

The transdermal route of administration for hormone replacement in postmenopausal women is a new way of reducing most of the undesirable effects of estrogenic therapies caused by the hepatic first-pass of oral administration.

Cyclical TTS-estradiol at a daily dose of 50 mcg is as effective in reducing menopausal symptoms as oral conjugated equine estrogens 0.625 mg. Assessment of its efficacy in preventing osteoporosis will have to wait for results of long-term studies.

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