Transdermal estrogen therapy in menopause

Eighteen months follow-up

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Summary: In this study we evaluated different metabolic parameters and bone mass, before and after 18 months of treatment by transdermal estradiol associated with oral sequential MPA in menopause.

We treated 46 physiologically postmenopausal patients (44-55 years old) for at least six months, by TTS/E2 50 mcg for 3 weeks and MPA 10 mg for the last 12 days of estradiol treatment. The fourth week was free of therapy.

Before treatment and after 18 months, we evaluated bone density (BMC/BW), body mass index (W/sqH), systolic and diastolic blood tension, lipid parameters, coagulation parameters, mineral metabolism, with statistical elaboration of our results.

After therapy we found a significant decrease in diastolic blood tension, a significant reduction in trygliceride levels and a slight but significant increase in HDL-cholesterol levels. The only variation in coagulation parameters was a decrease of circulating fibrinogen. No variation occurred in the body mass index, mineral metabolism or bone density.

In conclusion even long term transdermal treatment seems metabolically well tolerated and very useful in relieving neurovegetative climacteric symptoms and dystrophic genital ones.

Key words: Transdermal estrogen therapy; Metabolic parameters, bone mass.

INTRODUCTION

Over the last 90 years the average female life-span has been increasing up to 82 years and, according to actuarial estimates, will be around 85 at the end of this century; on the contrary, the average age for menopausal occurrence is still arund 47 years. The data suggest that about 94% of women born in the Sixties will be postmenopausal, and that 74% of them will survive for further 30 years ([1]).

Prevention and treatment of postmenopausal problems should consequently be mandatory, in order to assure the best possible life-quality to such a large population.

Currently, the best way to help these patients seems to be estrogen-progestin supply: climacteric as well as dystrophic symptoms are relieved, osteoporosis damage seems to be prevented, as well as that from cardiovascular disease; the risk/benefit ratio therefore appears very favourable, and the only contraindications for this treatment seem to be acute hepatopathies, nephrovascular hypertension, previous surgery for endometrial or breast cancer, and repeated thromboembolic accidents. On the other hand, chronic liver diseases and severe obesity should be considered relative contraindications ([2]).

Nowadays, estrogens are available in many different pharmaceutical prepara-

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tions, and can be administered by different routes: among them percutaneous, through transdermal systems which release the drug at a constant rate, seems to be very interesting. Indeed, transdermal admninistration may have some advantages, if compared to the oral one ([3]):

a) the hormone enters directly into the blood circulation, without undergoing metabolic transformation: this determines a constant estradiol plasma level, with a E1/E2 ratio like that of the fertile age ([4]);

b) hepatic first-pass and liver enzyme inductions are avoided: SHBG levels are not modified nor, consequently, are free estrogen levels; angiotensinogen and coagulation factor synthesis remains stable and blood tension and thromboembolic risk do not increase ([5]);

c) patient compliance seems highly increased, if compared to that with the oral of parenteral route: this may be explained by the easy use of transdermal systems and the ready disappearance of eventual side effects.

Currently, three transdermal systems are available, with different hormone contents:

– the smallest one delivers 25 mcg estradiol daily, through a 5 sqcm surface;

– the medium delivers 50 mcg estradiol daily, through a 10 sqcm surface;

– the largest, finally, delivers 100 mcg estradiol through a 20 sqcm surface.

Stable serum estradiol concentrations are reached within four hours from patch application for each of the three devices, and are around 23, 40 and 75 pg/ml estradiol according to the hormone content of the patch ([6]). Estradiol falls to basal values twenty-four hours after patch removal, and its half-life is about one hour.

The transdermal system is applied where skin is dry and hairless, best if on supero-external buttock quadrants or lower abdomen, and must be replaced every three and a half days. The skin area must be changed at every application.

However, in the patients with an intact uterus, progestin hormones should be added to estradiol ([7]), in that this protects against endometrial hyperplasia and cancer ([8]) without modifying the breast risk ([9]), and in that it helps in maintaining bone mineral content by reducing the rate of mineral loss ([10]).

MATERIALS AND METHODS

In this study we evaluated different metabolic parameters and bone mass, before and after 18 months of treatment by transdermal estradiol associated with oral sequential Medroxyprogesterone Acetate (MPA) in menopause.

We treated 46 patients physiologically postmenopausal for at least six months; their mean age ranged between 44 and 55 years.

The treatment consisted of the bi-weekly application of a transdermal system releasing 50 mcg estradiol daily for three weeks, and of the assumption of a daily oral 10 mg dose of MPA for the last 12 days of estradiol treatment. The fourth week was free of therapy.

Before treatment and after 18 months of hormonal supply we evaluated the values of the following parameters:

– bone density, expressed by the ratio BMC/BW and evaluated by single-photon densitometer (Norland mod. 2780) at the distal 1/10 of the radius;

– body mass index, expressed by the ratio W/sqH;

– systolic and diastolic blood tension;

– lipid parameters: total and HDL cholesterol, triglycerides, A1 and B apolipoproteins;

– coagulation parameters: PT, PTT, fibrinogen, ATIII;

– mineral metabolism: urinary Ca/Cr ratio, ALP, PTH, calcitonin.

The methods for the assays were those currently used at the Central Analysis Laboratory of Padua University Clinic.

The statistical evaluation of our results was performed by non parametric Wilcoxon Test.

RESULTS

After eighteen months of treatment, we found in our patients a significant decrease in diastolic blood tension ($p<0.05$) (Table 1), while systolic tension was unchanged; no variation occurred in the body mass index either.

Table 1. – *46 patients postmenopausal for at least 6 months; mean age 52 year (44-55); the parameters were evaluated before and after 18 month treatment with TTS-E2 50 mcg daily for 21 days plus MPA 10 mg os in the last twelve days, cyclically repeated after one week withdrowal.*

	0	18 months	Wilcoxon test
Body Mass Index	27.6±3.8	29.3±4.1	N.S.
Systolic Blood Pressure	132.5±8.9	130.4±7.1	N.S.
Diastolic Blood Pressure	88.4±5.2	81.3±4.8	$p<0.05$

Table 2. – *46 patients postmenopausal for at least 6 months; mean age 52 year (44-55); the parameters were evaluated before and after 18 month treatment with TTS-E2 50 mcg daily for 21 days plus MPA 10 mg os in the last twelve days, cyclically repeated after one week withdrowal.*

	0	18 months	Wilcoxon test
Tot Chol	195.3±18.4	203.4±23.7	N.S.
Triglycerides	110.4±12.7	98.9±14.3	$p<0.05$
HDL-Chol	58.6±8.4	61.3±7.4	$p<0.05$
Apo A-I	168.4±27.5	174.3±20.5	N.S.
Apo B	192.3±30.4	188.4±27.4	N.S.

As to lipid metaboism, we only observed a significant reduction in triglycerides levels ($p<0.05$) and a slight but significant increase in HDL chelesterol levels ($p<0.05$) (Table 2); total cholesterol and apoproteins did not vary.

The only variation among coagulation parameters was an increase in circulating Fibrinogen ($p<0.05$) (Table 3).

Finally, after eighteen months of estroprogestin treatment, no variation was found in the parameters of mineral metabolism (Table 4); bone density (BMC/BW, g/sqcm) increased around 1% in patients treated, while it decreased around 1% in 11 untreated controls (Fig. 1).

DISCUSSION AND CONCLUSIONS

Our results seem to agree with recent Literature, which points out that transdermal hormonal treatments do not affect metabolism significantly and are suitable for a safe supply for most postmenopausal patients ([11, 12, 13, 14, 15]).

The undesirable "limiting" effect of progestins on estrogen benefits was not confirmed by our study, in which MPA was administered, in agreement with other Authors ([16, 17, 18, 19]).

Our experience, moreover, suggests that transdermal treatment effectively relieves both neurovegetative climacteric symptoms and dystrophic genital ones; this relief is quite similar to that obtained by the oral route, but the patient compliance is so-

Table 3. – *46 patients postmenopausal for at least 6 months; mean age 52 years (44-55); the parameters were evaluated before and after 18 month treatment with TTS-E2 50 mcg daily for 21 days plus MPA 10 mg os in the last twelve days, cyclically repeated after one week withdrowal.*

	0	18 months	Wilcoxon test
PT	98.4±5.4	96.3±6.5	N.S.
PTT	26.5±5.1	25.7±4.8	N.S.
Fibrinogen	284.5±63.4	298.4±83.4	$p<0.05$
AT III	28.9±2.9	30.4±3.7	N.S.

Table 4. – *46 patients postmenopausal for at least 6 months; mean age 52 years (44-45); the parameters were evaluated before and after 18 month treatment with TTS-E2 50 mcg daily for 21 days plus MPA 10 mg os in the last twelve days, cyclically repeated after one week withdrowal.*

	0	18 months	Wilcoxon test
Urinary Ca/Cr	0.24±0.2	0.25±0.4	N.S.
Alkaline Phosphatase	98.40±12.4	96.50±11.7	N.S.
PTH	0.52±0.7	0.48±0.4	N.S.
Calcitonin	23.80±9.3	21.30±11.7	N.S.

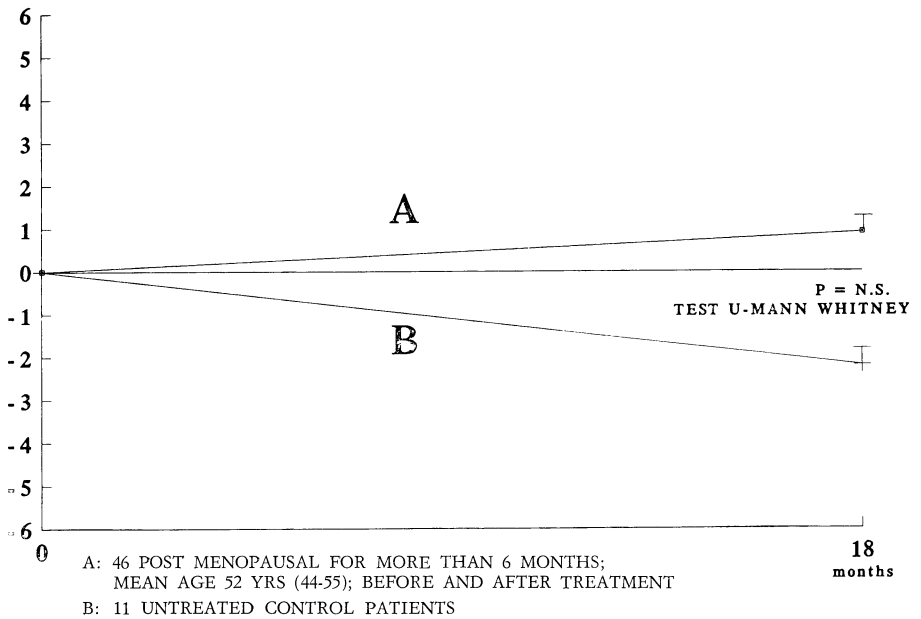

Fig. 1. – BMC/BW radius distal 1/10 (g/Sqcm).

metimes much better; the local and systemic tolerability, are in conclusion, very satisfactory.

Again, we also stress the need for balancing transdermal estrogens with progestins; they do not reduce estrogen benefits but prevent endometrial hyperproliferation, protecting breast tissue as well ([20, 21, 22]).

The prevention of bone demineralization obtained through the transdermal route is quite similar to that obtained through the oral one, while other parenteral routes (for instance the topic one) do not share the same effect ([23, 24]).

However, bone density variations around 1% such as those we observed cannot be considered significant, as the interscan variations range is around 1-3%; untreated patients trend, anyway, is towards decrement.

In conclusion, even long term transdermal treatments seem metabolically well tolerated; this will lead to further investigations aiming at improving our knowledges of their metabolic impact, in order to assure the optimal schedule for each single patient.

BIBLIOGRAPHY

1) Dati Istituto Scienze Mediche Milano, 1987.
2) Notelovitz M.: "Estrogen replacement therapy: indication, controindications and age selection". *AJOG, 161,* 1832, 1989.
3) Stumpf P. G.: "Pharmacokinetics of Estrogens". *Obst. Gyn., 75,* 145, 1990.
4) Judd H. L., Chetkowski R., Meldrum D., Steingold K., Eggena P., Randle R.: "Biological effects of transdermal estradiol: a comparative study". In: Lauritzen C.: "Transdermal estrogen substitution". Hans Huber Publishers; Toronto, 1987.
5) Whitehead M. I., Schenkel L.: "Transdermal Hormone Replacement". The Parthenam Publishing Granp Carnforth, 1990.
6) Powers M. S., Schenkel L., Darley P. E.: "Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta estradiol: comparison with conventional estrogens used for hormone replacement". *AJOG, 152,* 1099, 1985.

7) Whitehead M. I., Hillard T. C., Crook D.: "The role and use of progestogens". *Obst. Gyn., 75,* 595, 1990.
8) Gambrell R. D.: "Use of progestogen therapy". *AJOG, 156,* 1304, 1987.
9) Hammond C. B., Jelovsek F. R., Lee K. L., Creasman W. T., Parker R. T..: "Effects of long-term estrogen replacement therapy". *AJOG, 133,* 537, 1979.
10) "Consensus development conference on Prophylaxis and treatment of osteoporosis". *Brit. Med. J. (Clin. Res.), 295,* 914, 1987.
11) Padwick M. L., Endacott J., Whitehead M. I.: "Efficacy acceptability and metabolic effects of transdermal estradiol in the management of postmenopausal women". *AJOG, 152,* 1085, 1985.
12) Lkjaersig N. A., Fletcher A. P., Steingold K. A., *et al.:* "Blood coagulation in postmenopausal women given estrogen treatment: comparison of transdermal and oral administration". *J. Lab. Clin. Med., 111,* 224, 1988.
13) Jensen J., Riis B. J., Cristhiansen C. *et al.*: "Long term effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women". *AJOG, 156,* 66, 1987.
14) De Lignieres, Basdevant A., Thomas G. *et al.:* "Biological effects of estradiol 17-beta in postmenopausal women: oral versus percutaneous administration". *J. Clin. Endocrinol. Metab. 62,* 536, 1986.
15) Holst J., Cajander S., Calstrom K. *et al.*: "A comparison of liver protein induction in postmenopausal women during oral and percutaneous estrogen replacement therapy". *Brit. J. Obst. Gyn., 90, 355,* 1983.
16) Hirvonen E., Halkonen M., Manninen V.: "Effects of different progestogens on lipoproteins during postmenopausal replacement therapy". *N. Eng. J. Med., 304,* 560, 1981.
17) Campbell S., Whitehead M. I.: "Potency and hepato-cellular effects of estrogens after different routes of administration". In: van Keep, Utiam W., eds.: "The controversial climateric". Lancaster England MTP Press, 103, 1982.
18) Fahraeus L., Wallentin L.: "High density lipoprotein subfractions during oral and cutaneous administration of 17 beta estradiol to postmenopausal women". *J. Clin. Endoc. Metab., 56,* 797, 1983.
19) Elikik F., Compel A., Bodard M. *et al.*: "Effects of percutaneous estradiol and conjugated estrogens on levels of plasma-proteins and triglycerides in postmenopausal women". *AJOG, 143,* 88, 1982.
20) Gambrell R. D. j, Maier R. C., Sanders B. I.: "Decreased incidence of breast cancer in postmenopausal estrogen/progestogen users". *Obst. Gyn., 62,* 435, 1983.
21) Whitehead M. I., Campbell S.: "Endometrial histology, uterine bleeding and oestrogens levels in menopausal women receiving oestrogen therapy and oestrogen/progestogen therapy". In: Brush M. J., Taylor R. M., King R. B. J., eds: "Endometrial cancer", London, p. 65, 1978.
22) Whitehead M. I., Townsend P. T., Pryse D. J. *et al.:* "Effects of estrogens and progestins on the biochemistry and morfology of the postmenopausal endometrium". *N. Eng. J. Med., 305,* 1599, 1981.
23) Adami S., Suppi R., Bertoldo F. *et al.*: "Transdermal estradiol in the treatment of postmenopausal bone loss". *Bone and Mineral 7,* 79, 1989.
24) Lindsay R., Har D. M., Clark D. M.: "The minimum effective dose of estrogen for prevention of postmenopausal bone loss". *Obst. Gyn., 63,* 759, 1984.

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