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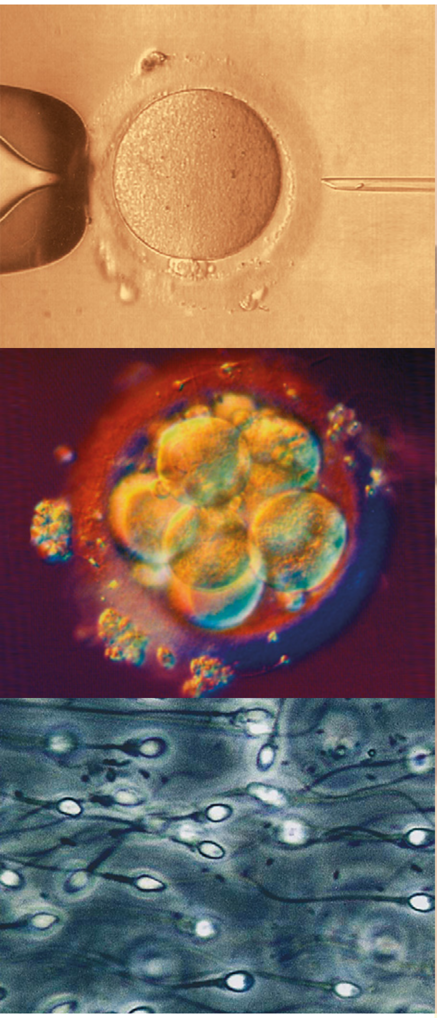

Estetrol, a Fetal Steroid for the Treatment of Adults

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Estetrol, a Fetal Steroid for the Treatment of Adults

H. J. T. Coelingh Bennink, J.-M. Foidart

on behalf of Pantarhei Bioscience, the Netherlands and Mithra Pharmaceuticals, Belgium

Estetrol (E_4) is a natural fetal estrogen. This steroid molecule has been discovered in 1965 by the group of Egon Diczfalusy at the Karolinska Institute in Sweden and as a drug for human use in 2001 by the group of Herjan Coelingh Bennink at Pantarhei Bioscience in the Netherlands. Estetrol is structurally closely related to the predominant natural estrogens estron (E_1), estradiol (E_2) and estriol (E_3), but with a number of different and potentially favorable features.

In comparison to E_2, E_4 displays much higher bioavailability upon oral administration and its elimination is considerably slower. Moreover, E_4 is a metabolic endproduct and not metabolized into other estrogenic metabolites as happens after oral intake of E_2. Consequently, stable therapeutic blood concentrations are rapidly achieved upon oral administration. *In vitro* E_4 has been shown to interact exclusively with the estrogen receptors with some preference for the alpha receptor. Estetrol interacts minimally with liver function and steroid- and drug-metabolizing liver enzymes, suggesting among others less interference with hemostasis compared to other estrogens and potentially a lower risk of venous thromboembolism (VTE). These features indicate the particular feasibility and anticipated safety of E_4 as an oral therapy in a once-daily dosing regimen.

Data from preclinical pharmacology studies support the safe use of E_4 in humans and suggest therapeutic effects such as menopausal hormone treatment (MHT) of vasomotor symptoms (VMS) and vulvovaginal atrophy (VVA), prevention of osteoporosis, as well as application in contraceptive regimen. Estetrol antagonized E_2 in *in vitro* models and prevented and inhibited growth of mammary tumors in an experimental rat model, suggesting a more breast-friendly profile compared to other estrogens and suitability of E_4 as estrogen add-back treatment during anti-hormonal endocrine therapy of breast cancer, endometriosis and prostate cancer.

After 28-days daily oral administration of 2, 10, 20, or 40 mg to postmenopausal women, E_4 has been shown to reduce the occurrence of VMS, to reverse the menopause-induced VVA and to exert bone-preserving changes by decreasing bone turnover, especially bone-resorption, suggesting positive bone formation. Endometrial proliferation, to an extent similar to 2 mg E_2-valerate (E_2V), was found at E_4 doses of 10 mg/day. Estetrol was safe and had minimal effects on the synthesis of lipoproteins, SHBG and parameters of hemostasis, supporting the favorable profile with respect to VTE. At present dose-finding studies with E_4 are prepared for the treatment of VMS and VVA.

Estetrol at a daily oral dose of 15 or 20 mg has been shown to be suitable as the estrogen component of combined oral contraceptives in a full phase II development program in collaboration with Jean-Michel Foidart in Belgium, demonstrating excellent efficacy, safety and cycle control, while minimally interfering with a number of metabolic parameters. Further phase III development of the oral contraceptive application of E_4 will be performed by Mithra Pharmaceuticals in Liège, Belgium. **J Reproduktionsmed Endokrinol_Online 2015; (4): 399–401.**

Key words: Estetrol, E_4, natural fetal estrogen, contraception, VMS, VVA, add-back treatment

Introduction

The estrogen Estetrol (E_4) is produced in large quantities by the fetal liver during human pregnancy only. The molecule was discovered in 1965 at the Karolinska Institute in Stockholm [1]. Estetrol differs from other natural estrogens by an additional alpha-hydroxy (OH) group at position 15 of the molecule. It has been demonstrated that this minor structural difference has important implications, since this single additional OH group as compared to estriol (E_3) extends the elimination half-life in the human from 10 minutes for E_3 to 20–28 hours for E_4 [2]. The half-life of E_4 is also much longer than those of other natural estrogens, including natural 17β-estradiol (E_2) and micronized E_2, for which half-lifes of 1–2 hours and 10–12 hours have been reported respectively. In addition, E_4 is more efficiently absorbed than E_2 upon oral administration, as it is much less subject to pre-systemic and first-pass metabolism. These features of E_4 are important prerequisites for the development of a once-a-day oral drug. Being a natural estrogen excreted abundantly in the urine of pregnant women, the development of a drug containing E_4 is not expected to carry additional environmental risks.

Preclinical Development

Pantarhei Bioscience has discovered that E_4 is suitable as a drug for human use. Pantarhei first demonstrated that E_4 is orally bioavailable in the rat with a remarkably long elimination half-life for the rat of 2–3 hours [3]. Subsequently the pharmacological profile of E_4 was characterized in detail in a number of studies. In these studies, E_4 was administered orally and compared to oral ethinyl-estradiol (EE), a synthetic estrogen. Comparison with E_2 and E_3 was not feasible given the rapid deactivation of these natural estrogens by the rat liver. The results of Pantarhei's pharmacological studies indicate that E_4 acts as an estrogen on the vagina [3], the uterus [3] and bone [4]. Estetrol shows limited interaction with the liver, both kinetically and dynamically [5]. Furthermore, E_4 was found to suppress the naloxone-induced tail skin temperature increase, an experimental model of hot flushes [6], and to inhibit ovulation [7]. Estetrol has a vaso-relaxing effect on isolated rat arteries [8]. The effect on breast tumor tissue is summarized later in this paper.

In *in vitro* studies, Pantarhei has demonstrated that E_4 is capable of binding to both ER-alpha as well as ER-beta, with a four- to fivefold preference for ER-alpha. Estetrol displayed a relatively low affinity compared to EE and E_2, but E_4 did not bind to other steroid receptors and to a panel of 130 other drug targets [5].

Metabolism of E_4 in human liver cells was found to be slow. Importantly, and in agreement with historical isotope studies carried out in the early seventies, no active metabolites of E_4 have been detected to date, and E_4 is excreted in an inactive form by the liver and kidney following conjugation to sulphate and/or glucuronide [5]. In this respect E_4 substantially differs from E_2, which after oral administration is extensively metabolized, predominantly into estrone (E_1) and estrone sulphate (E_1S), as well as into a large

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number of other E_1- and E_2-derived metabolites [9].

As expected in view of the high levels of E_4 during human pregnancy, E_4 seems to be very safe. In animal pharmacology studies, in which doses of up to 10 mg/kg/day were used for four weeks, E_4 did not cause any relevant side effect. The safety profile of E_4 was further confirmed in a number of studies addressing the interaction of E_4 with human hepatocytes [5], which is of particular significance given the known and well-documented side effects and interactions of estrogens on liver function. Contrary to EE and E_2, E_4 did not increase the synthesis of Sex Hormone Binding Globuline (SHBG) and did not change the activity of the five most relevant Cytochrome P-450-related liver enzymes [5]. Furthermore, and different from other estrogens, E_4 appeared not to bind to SHBG [10].

Extensive information on the history and the preclinical and clinical profile of E_4 is available in several review papers [11–14] and most of the pharmacological studies performed by Pantarhei have been published in Supplement I of the journal *Climacteric* in 2008.

Toxicology

A complete toxicology program was performed in rat and monkey. The results showed that the toxicology of E_4 is largely determined by its estrogenic action, leading to exaggerated pharmacological responses at excessively high exposures. No specific toxicity of E_4 has been observed.

Clinical Development Phase I/IIA

A single rising dose phase IA study has been performed in healthy post-menopausal women. Estetrol showed high and dose-proportional oral bioavailability with a long elimination half-life of 28 hours [2], thereby confirming its potential as an oral therapeutic. A dose-dependent peak was found to occur within 15 to 30 minutes after oral administration, which was followed by a sharp decline of the E_4 blood level and a secondary rise and slow elimination of E_4 thereafter, suggesting gastro-intestinal recirculation. No side effects were observed.

Pharmacokinetic simulations have shown that the 24-hour exposure of the human fetus to E_4 at term pregnancy equals a daily human oral dose of 50–55 mg E_4, suggesting that such a dose may be expected to be safe in the human.

A multiple rising dose phase IB/IIA study with E_4 was performed in healthy postmenopausal women to evaluate safety, pharmacokinetics and pharmacodynamic parameters. Doses of 2, 10, 20 and 40 mg E_4 were evaluated after daily oral administration for 28 days and the lowest 2 mg dose of E_4 was compared head-to-head with 2 mg estradiol-valerate (E_2V).

Estetrol at an oral dose of 10 mg/day for a short period of 28 days was shown to be effective in reducing (~ 40%) the frequency of hot flushes (HF) in women suffering from such complaints. Estetrol appeared somewhat more effective than E_2V 2 mg/day. Full evaluation of the effect of E_4 for vasomotor symptoms (VMS) requires treatment periods of at least 12 weeks.

Vaginal cytology revealed dose-dependent estrogenic effects (vaginal maturation), with a dose of 2 mg E_4 per day E_4 showing similar effects as E_2V 2 mg/day. In the case of vulvovaginal atrophy (VVA) the full estrogenic effect of E_4 was obtained after 4 weeks treatment already.

Ultrasound measurement of endometrial thickness did not show an effect of E_4 at 2 mg/day, in contrast to E_2V 2 mg/day and E_4 10 mg/day. Biopsies taken from subjects displaying a > 50% increase in endometrial thickness revealed the expected proliferative changes. This data suggest that low dose oral E_4 treatment of VVA may not require endometrial progestin protection, but higher doses of E_4 will require a progestin. To avoid the increased breast cancer risk related to the use of oral progestins, higher doses of E_4 should preferably be combined with an intra-uterine levonorgestrel-releasing intra-uterine device (IUD) or with the progestin dydrogesterone, which is the progestin closest to natural progesterone.

Estetrol was associated with a dose-dependent decrease in the levels of osteocalcin and type I collagen telopeptide (CTX-1), parameters of bone formation and bone resorption respectively. Daily oral doses of 10 mg E_4 decreased levels of CTX-1 to a similar extent as E_2V 2.0 mg/day, whereas the decrease of osteocalcin with E_4 was much less, suggesting a net effect and positive bone formation. This may qualify E_4 not only for prevention, but also for treatment of osteoporosis.

Estetrol in the oral dose range of 2–10 mg/day for a period of 28 days had minimal effects on liver-protein synthesis. At 2.0 mg/day no effect on SHBG was observed, while at 10 mg/day similar effects as induced by 2.0 mg/day E_2V were observed. E_4 did not affect the synthesis of triglycerides, in contrast to E_2V, and was furthermore associated with no changes or small decreases in LDL-cholesterol (considered favorable) and total cholesterol, a small and favorable increase in HDL-cholesterol and a resulting small decrease in the ratio cholesterol/HDL-cholesterol. Hemostatic factors and activities, including F1+2, tPA and nAPCr, were all minimally influenced, suggesting a limited effect on the risk of VTE.

No serious adverse events occurred at any E_4 dose, and no significant changes were observed in vital signs, body weight, physical examination or ECG-readings either.

Estetrol may be suitable as the estrogen in combined oral contraceptives (COCs), for the treatment of menopausal symptoms, for prevention of osteoporosis and for estrogen add-back therapy during treatment with aromatase inhibitors and tamoxifene in women with breast cancer and in men with prostate cancer treated with GnRH analogues.

Combined Oral Contraception (COC)

A complete phase II clinical development has been performed for oral contraception. In summary, E_4 inhibits ovulation effectively when combined with a standard COC dose of a progestin [15]. Estetrol COCs have better cycle control than the E_2/dienogest comparator. Its safety profile is favorable in phase I and phase II clinical trials. No relevant side effects have been observed in more than 300 women taking 15 or 20 mg E_4 for six COC cycles in combination with a progestin.

Estetrol has significantly less effect on liver [16] and hemostasis parameters compared to EE and E_2, whatever the progestin used in the combination, suggesting a lower risk of VTE compared to other COCs. Estetrol seems a more breast-friendly estrogen, since it exhibits estrogen-antagonistic effects in preclinical and clinical studies, especially in the presence of E_2. Moreover, in contrast to orally administered E_2, E_4 does not yield a large pool of E_1S, which constitutes a potential source of unwanted E_2-resynthesis in the breast.

Menopausal Hormone Therapy (MHT)

According to the present standard of care for MHT, Pantarhei has focused on oral E_4 treatment of early post-menopausal women with moderate to serious complaints due to estrogen deficiency such as hot flushes and sweatings, urogenital atrophy, dyspareunia caused by vaginal dryness, arthralgia, loss of bone mass and an increased risk of fractures and decreasing cognition.

Major clinical advantages of E_4 in MHT compared to presently used estrogens are a lower incidence of side effects and lower risks of VTE and gallbladder disease. In addition the estrogen-antagonistic effect of E_4 on the breast may result in a better safety profile in relation to breast cancer (BC).

Since the oral synthetic progestins seem to be more important than the estrogens for the risk to develop BC, the objective is to develop MHT drugs without addition of a progestin. This will be achieved by developing a low dose of oral E_4 for VVA that does not stimulate the endometrium and therefore does not require addition of a progestin. For VMS a higher dose of oral E_4 may be required, that will induce endometrial proliferation. To protect the endometrium and to avoid oral progestins and their increased BC risk, an intra-uterine levonorgestrel-releasing IUD is preferred.

Vasomotor Symptoms (VMS)

The therapeutic potential of E_4 for the treatment of VMS is supported by Figures 1 and 2.

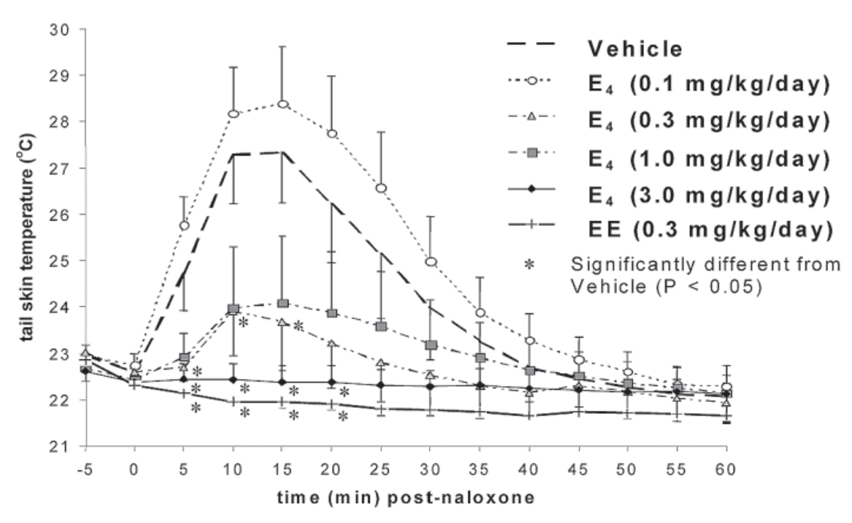

Figure 1. In the rat hot flush model E_4 causes a dose dependent decrease of the naloxone induced tail temperature raise. Mod. from [6]. © Pantarhei Bioscience.

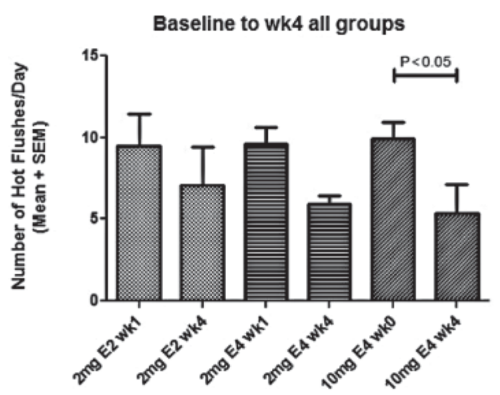

Figure 2. Doses of 2 and 10 mg E_4 cause a significant decrease of the number of hot flushes in postmenopausal women, whereas both doses are as effective as the 2 mg dose of the comparator E_2V. © Pantarhei Bioscience.

Figure 1 shows the dose-related effect of E_4 in an experimental hot flush model in the rat. Complete inhibition of the tail temperature rise is obtained at a dose-level 10× higher than EE.

Figure 2 shows the effect of E_4 on hot flushes in the multiple rising dose phase IB/IIA study in postmenopausal women with at least 50 hot flushes per week (the FDA criterion). In this 28-day-study E_4 is as effective as E_2V. As mentioned before, the final judgement of efficacy of E_4 requires a treatment period of at least 12 weeks. Such a 12-week E_4 dose-finding study in women with moderate to severe vasomotor symptoms is needed to estimate the optimal dose of E_4 for this application.

Vulvovaginal Atrophy (VVA)

The therapeutic potential of E_4 for the treatment of VVA is supported by Figure 3 and Table 1.

Figure 3 shows that in the Allen-Doisy test all doses of E_4 induce full vaginal cornification in the ovariectomized (OVX) rat.

For use in the human this suggests that a very low dose of E_4 may be effective, although the time to achieve the full effect may be somewhat longer compared to higher doses of E_4.

Table 1 shows the effect of E_4 on the vaginal cytology in the multiple rising dose phase IB/IIA study in postmenopausal women. In this 28-day-study E_4 has the full effect and is as effective as E_2V.

Add-back Treatment

The terminology “add-back treatment” is used for adding back an estrogen after complete pharmacological suppression of endogenous estrogen synthesis by anti-estrogenic treatment of diseases such as breast and prostate cancer and serious

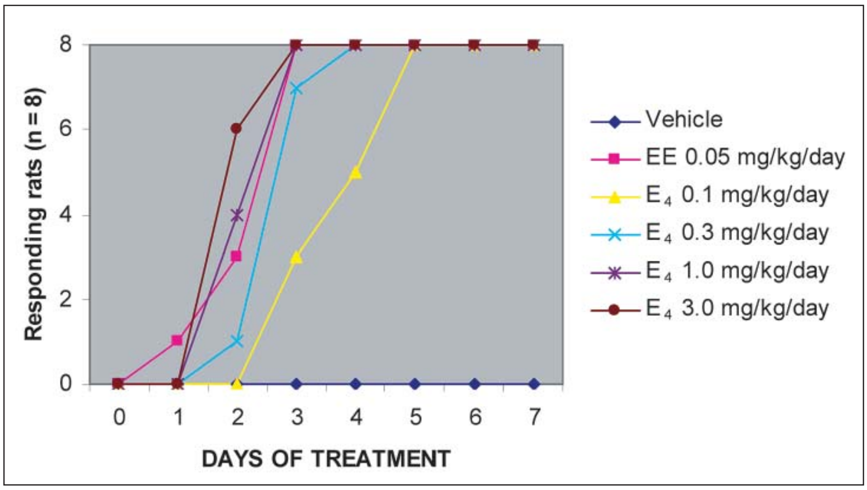

Figure 3. E_4 induces cornification of the vaginal epithelium in ovariectomised rat with all doses tested. Lower doses are also effective, but require more time to achieve the full effect. Mod. from [3]. © Pantarhei Bioscience.

Table 1. After 28 days of E_4 treatment in early postmenopausal women, all E_4 doses (2, 10 and 20 mg/day) induce a normal physiological cytology of the vagina with a low percentage of parabasal cells and high percentages of intermediate and superficial cells. The effect is comparable to 2 mg E_2V. © Pantarhei Bioscience.

	Parabasal (%)	Intermediate (%)	Superficial (%)
E_2-val – 2 mg	0 (0–3)	74 (51–92)	26 (15–49)
E_4 – 2 mg	2 (0–15)	80 (53–94)	18 (6–47)
E_4 – 10 mg	8 (0–17)	45 (23–78)	47 (5–77)
E_4 – 20 mg	0 (0)	60 (17–88)	40 (12–83)

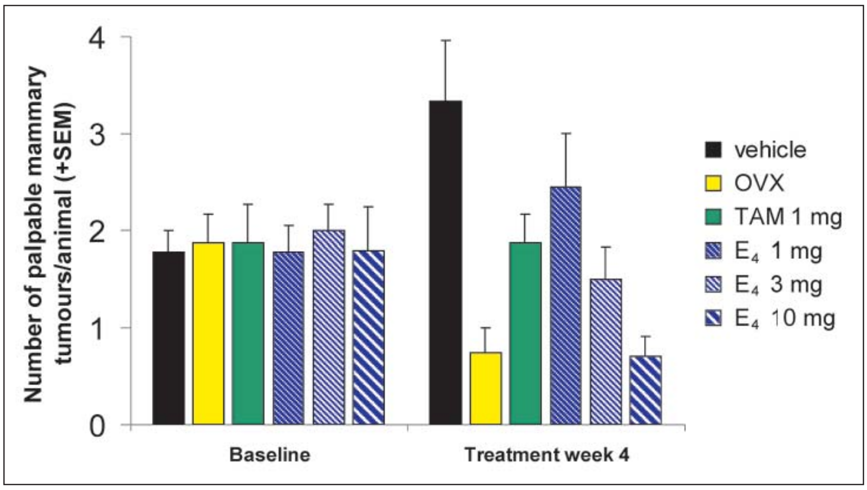

Figure 4. The therapeutic potential of E_4 to inhibit growth of pre-existing mammary tumors was investigated in the DMBA rat model. Eight weeks after tumor induction, animals that had developed palpable mammary tumors were either ovariectomized (OVX) or treated orally with a vehicle (saline administration only), tamoxifene (TAM), or different doses of E_4 (1 mg, 3 mg and 10 mg; all per kg) daily during four weeks. The number of palpable mammary tumors before ("Baseline") and after ("Treatment Week 4") four weeks of treatment was compared. Standard errors of the mean are indicated. A significant disappearance of mammary tumors was observed after ovariectomy and dose-dependently after E_4 treatment. With the dose of TAM used (1 mg/kg) no increase or decrease was observed, but higher doses of TAM may be effective. Mod. from [17, 18]. © Pantarhei Bioscience.

endometriosis. Since the side effects of removing estrogens are often unacceptable and interfere with compliance to the anti-estrogenic drugs, adding back an estrogen at a low dose has been introduced as a solution for this problem. Actually one may consider add-back treatment as a special type of MHT.

As Pantarhei has demonstrated in pharmacological and clinical studies that E_4 acts as an estrogen agonist on vagina [3], bone [4] and brain [6], whereas E_4 has estrogen-antagonistic effects on breast tumor tissue (see below), the mixed agonistic/antagonistic profile of E_4 seems highly attractive for its use as estrogen add-back treatment in combination with anti-estrogenic treatments such as aromatase inhibitors, tamoxifene and GnRH analogues.

Preclinical Studies related to Breast Cancer

During the pharmacological profiling of E_4 in human breast cancer (BC) cell lines and in the DMBA rat model, Pantarhei has demonstrated that E_4 can act as an estrogen antagonist in breast tumor tissue.

The estrogen antagonism of E_4 has been confirmed in in vitro models by the groups of Gompel in Paris, Simoncini and Genazzani in Pisa and Greene in Chicago.

In three separate experiments in the DMBA animal model, Pantarhei has shown that E_4 can dose-dependently prevent and treat breast tumors [17, 18]. Figure 4 shows data from the DMBA treatment study demonstrating that E4 at the highest dose (10 mg/kg) removes breast tumors as effectively as OVX. Even when this effect would have been obtained by complete suppression of ovarian function and extinction of E_2 only, it shows that E_4 at a high dose does not promote tumor growth. However it is more likely that the effect of E_4 at this dose is a cytotoxic effect, also known from other estrogens such as EE, E_2 and DES at high doses. A major difference with these other estrogens is the expected superior tolerability of E_4 at higher doses, allowing the clinical use of E_4 at such high dose levels.

Very recently the group of Foidart in Liége has demonstrated that E_4 is acting as an estrogen via the genomic pathway, whereas it acts as an anti-estrogen via the non-genomic pathway [19]. This unique combination of properties classifies E_4 as the first known natural SERM (selective estrogen receptor modulator) and explains why in preclinical and clinical studies E_4 exhibits anti-estrogenic effects on breast cancer. It implies that E_4 might be safer for the breast than other estrogens. This, in combination with the liver-friendly profile of E_4 and its very favorable safety profile, suggests that E_4 containing new drugs are expected to exhibit a very beneficial benefit-risk ratio.

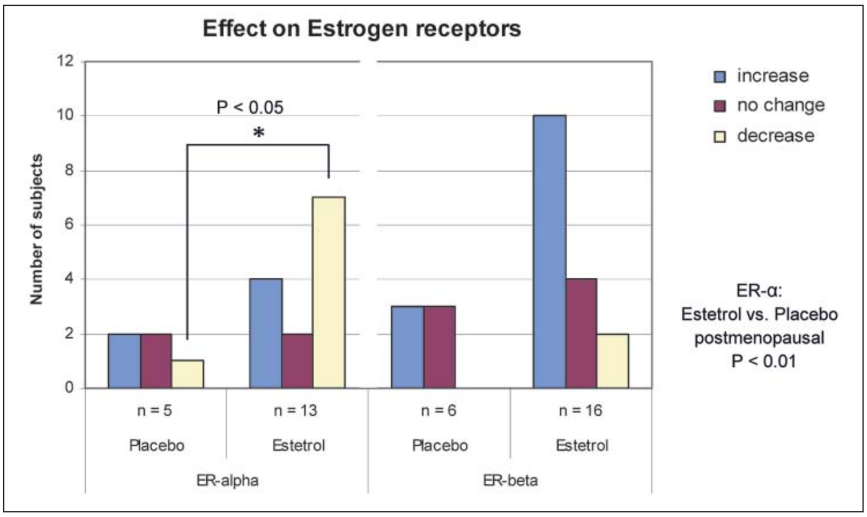

Figure 5. The effect of E_4 on estrogen receptors in breast tumor tissue. © Pantarhei Bioscience.

Clinical Study in Women with Breast Cancer

A prospective, double-blind, placebo-controlled, randomised, 14 days, pre-operative, neo-adjuvant study was performed in 15 pre- and 15 postmenopausal women with estrogen-receptor positive early BC in the "Vienna General Hospital", Austria. Results have been published recently [20] and showed that E_4 had a significant pro-apoptotic effect on tumor tissue while Ki67 expression remained unchanged. Estetrol increased SHBG significantly thereby reducing the concentrations of bioavailable E_2. FSH levels decreased in postmenopausal women only and LH levels remained unchanged. Systemic IGF-1 levels decreased significantly. The most intriguing finding of the study was that intratumoral epithelial ER-alpha expression decreased significantly and a trend was found towards an increased expression of ER-beta (Fig. 5). Since ER-alpha is related to proliferation and ER-beta to anti-proliferation, the observed effect of E_4 may offer an additional explanation for the unexpected estrogen-antagonistic effect of E_4.

Estetrol add-back in Breast Cancer treated with Aromatase Inhibitors or Tamoxifen

Based on its antagonistic activity in breast tissue, E_4 has the potential to be developed for add-back treatment in breast cancer in estrogen receptor (ER) positive patients treated with aromatase inhibitors (AI's) or tamoxifene. Estrogen add-back has the purpose to counteract the serious side effects caused by the extreme estrogen deficiency induced by the AI's and tamoxifen (hot flushes, vaginal dryness, bone loss, arthralgia, cognition problems). However it should not interfere with the efficacy of the AI's and tamoxifen. The combination of E_4 with an AI seems especially attractive, since the mechanism of action of both drugs is entirely different i.e. receptor antagonism and inhibition of synthesis respectively. The combination might even prove to be complementary when E_4 would have estrogen-antagonistic effects under these conditions.

Estetrol add-back in Prostate Cancer treated with GnRH Agonists

GnRH agonists are used for antihormonal treatment of prostate cancer (PC) by inhibition of the gonadotrophins FSH and especially LH, which stimulates the synthesis of testosterone, that stimulates tumor growth. Also in males this type of treatment causes typical "climacteric-like" complaints caused by estrogen deficiency such as hot flushes and sweatings, arthralgia, loss of bone mass, an increased fracture risk and cognition problems. These "climacteric-like" problems might be counteracted by E_4 treatment.

In addition, the inhibitory effect of E_4 on gonadotrophins may support the effect of the GnRH agonist. Estetrol may even suppress or inhibit the unwanted initial rise of gonadotrophins occurring at the start of GnRH agonist treatment and therefore E_4 seems the perfect match for estrogen add-back in men with PC.

Conflict of Interest

H. J. T. Coelingh Bennink is the inventor of E_4 and CEO and shareholder of Pantarhei Bioscience, the company developing E_4 for several human applications in collaboration with Mithra Pharmaceuticals, consulted by J.-M. Foidart.

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