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The effects of the human fetal estrogen estetrol (E4) in healthy men to estimate its potential use for the treatment of prostate cancer

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* Potential conflict of interest may exist. Refer to the ENDO 2017 Meeting App.

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Introduction

Estetrol (E4) is an estrogen, produced exclusively by the human fetal liver during pregnancy. This steroid is orally bioavailable and has little interaction with the liver. E4 has few side effects and can therefore be administered in high doses. E4 has been developed by Pantarhei Bioscience from 2001 to 2015. At present E4 is in phase I/II development for the treatment of breast cancer by Pantarhei Oncology. Prostate cancer is another indication that is identified for E4 by Pantarhei Oncology. E4 is in phase III development for oral contraception and in phase II for menopausal hormone therapy by Mithra Pharmaceuticals.

Hormone therapy, also called androgen deprivation therapy (ADT) is central to the management of prostate cancer. This treatment is based on the reduction/elimination of the growth promoting effects of androgens, especially testosterone (T). However, ADT not only suppress T, but also estrogens, which affects quality of life and causes multiple side effects. E4 is expected to prevent the signs and symptoms of estrogen deficiency caused by the T suppression, for instance osteoporosis, bone fractures, hot flushes, sweatings, arthralgia, mood, sleep and cognition disturbances. In addition, E4 is expected to have suppressive effects on T levels itself.

Study Objective

The objective of the study was to investigate the efficacy and safety of E4 for its potential use in the treatment of prostate cancer with special emphasis on the effect of E4 on testosterone (T) levels.

Design

The effects have been investigated in a phase Ib randomized, double-blind, placebo-controlled, multiple rising dose study in healthy men.

Materials & Methods

The study was performed by the CRO QPS Netherlands BV (Groningen, The Netherlands), under the supervision of T. Mensinga, MD, PhD, and was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practices (NCT02718378).

Participants were non-smoking, healthy, middle aged men between 40-70 years with a BMI between 18.5-30.0 kg/m^2 and a PSA value <3.0 ng/ml at screening. Participants were allocated to the active treatment or placebo treatment in a 2:1 ratio. Three dose levels have been tested in cohorts of 15 men each. Dose levels were 20 mg E4, 40 mg E4 and 60 mg E4. Treatment period was 28 days. The E4/placebo tablets were taken orally.

Study parameters measured were:

- Endocrine efficacy parameters: total T, free T, SHBG, LH, FSH, E2
- E4 for PK analysis
- Biochemical safety parameters: hemostasis parameters, lipids, glucose, bone turnover markers
- Clinical safety parameters: body weight, vital signs, ECG, physical examination, routine safety parameters and monitoring of (S)AEs.

All safety parameters and the endocrine parameters are summarized descriptively.

Study Results

In total 45 healthy men were randomized and started the study. Two men dropped out. One subject (receiving 60 mg E4) stopped in the second week of treatment, one subject (receiving placebo) stopped after the 28 day treatment period. Reason for drop out of both subjects was not related to the (use of) study medication.

The results show that:

- Total and free T levels decreased with E4 intake (see Figure 1).
- SHBG levels increased with E4 intake (see Figure 1).
- Differences between 40 mg E4 and 60 mg E4 on the total T, free T and SHBG levels were small.
- FSH and E2 levels decreased with E4 intake (see Table 1).
- LH levels showed a rapid decrease after administration of E4. Levels returned to baseline values before intake of the next dose.
- AEs: nipple tenderness and libido decrease were most frequently reported.
- Safety: no clinically relevant change in vital signs, ECG and physical examination. No change in body weight.
- Lipids: favorable effects with E4 intake.
- Hemostatic variables: little changes with 20 mg E4. With 40 and 60 mg E4 some parameters show changes comparable to those with third generation oral contraceptives in women.

Study Results

Table 1. Mean (± SD) values for endocrine parameters at baseline and after treatment

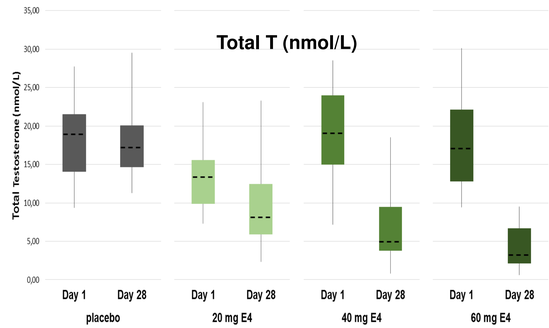
	Placebo	20 mg E4	40 mg E4	60 mg E4
Total T, nmol/L				
Day 1	18,57 ± 5,54	13,28 ± 4,83	18,30 ± 7,16	18,25 ± 6,70
Day 28	17,71 ± 4,85	9,54 ± 6,39	7,30 ± 5,47	4,37 ± 3,26
Free T, nmol/L				
Day 1	0,17 ± 0,04	0,14 ± 0,05	0,12 ± 0,03	0,19 ± 0,06
Day 28	0,17 ± 0,04	0,08 ± 0,06	0,02 ± 0,02	0,03 ± 0,03
SHBG, nmol/L				
Day 1	42,31 ± 11,12	31,08 ± 6,89	48,01 ± 18,55	43,80 ± 16,75
Day 28	43,77 ± 13,33	48,61 ± 15,55	97,67 ± 30,24	96,77 ± 41,83
FSH, U/L				
Day 1	6,63 ± 2,98	5,92 ± 6,22	6,57 ± 4,44	6,24 ± 2,57
Day 28	6,81 ± 2,980	1,88 ± 1,14	1,08 ± 0,93	0,63 ± 0,37
LH, U/L				
Day 1	4,81 ± 1,92	4,57 ± 2,25	4,06 ± 1,46	5,56 ± 2,22
Day 28	5,63 ± 1,57	4,77 ± 1,26	4,73 ± 1,66	3,56 ± 1,78
E2, pmol/L				
Day 1	78,73 ± 16,53	64,57 ± 19,52	77,96 ± 17,65	80,78 ± 24,35
Day 28	81,99 ± 19,25	45,24 ± 29,65	29,39 ± 11,74	23,80 ± 8,33

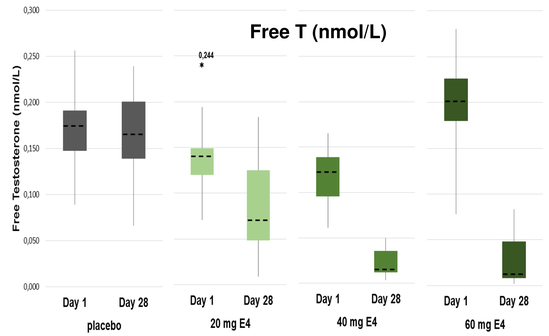
E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; T, testosterone

In Figure 1, the box and whisker plots, half of the data (percentile 25-75) is represented by the boxes. Dark dashed lines in the boxes indicate the median. T-bars from the boxes extend to the minimum and maximum. In the Free T plot the star represents an outlier, defined as a value more that three times the height of the box.

Conclusions

- **A daily dose of 20 mg, 40 mg or 60 mg E4 was well tolerated by healthy men aged 40-70 years. Libido decrease and nipple tenderness were the side effects which were most frequently reported.**
- **The observed dose-response related decrease of total and free T levels and the acceptable safety parameters suggest that E4 may be suitable for a combination treatment with ADT.**





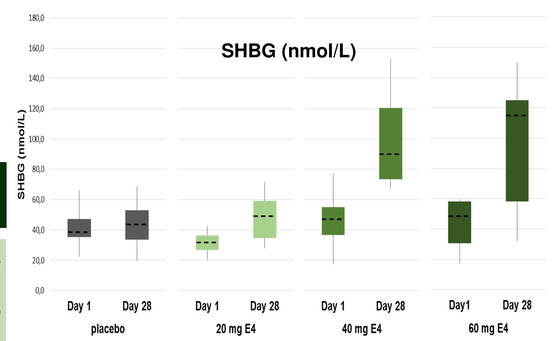


Figure 1 Total T, Free T and SHBG levels before and after treatment with E4

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