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English Translated

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PHARMACOKINETICS OF ESTRADIOL VALERATE IN POSTMENOPAUSAL WOMEN AFTER INTRAMUSCULAR ADMINISTRATION

Summary [English Abstract]

Limited information is available on the effects of intramuscular applicated 5 mg estradiol on estradiol and estrone levels and the estradiol-estrone quotient. In the present study this estradiol dose in postmenopausal women has been investigated. Participants: 17 healthy postmenopausal women without former hormone replacement therapy. 17β-estradiol (E2), estrone (E1), FSH, LH, and prolactin were determined before a single intramuscular injection of 5 mg estradiol valerate, four hours after injection and then every other day, that is on the 3rd, 5th, 7th, 9th, and 11th days. Four hours after the injection there was already a significant increase in estradiol and estrone which continued up to the 3rd to 5th day. After this, the levels of both estrogens fell slowly and continuously, that of estradiol more markedly than that of estrone. The course of the estradiol and estrone curves was practically synchronous with the estrone level always higher than the estradiol level. Intramuscular applicated 5 mg estradiol valerate induced effective serum estradiol levels. Estrone is the dominant estrogen in the postmenopause even after intramuscular administration of estradiol, independent of the body mass index.

Key words: pharmacokinetic, estradiol, estrone, FSH, LH

SUMMARY [German Translated Abstract—Different/Longer]

17 postmenopausal women with healthy metabolism were treated with 17β-estradiol before a single intramuscular application of 5 mg estradiol valerate and four hours afterwards and then every 2nd day on the 3rd, 5th, 7th, 9th, and 11th day estradiol (E2), estrone (E1), FSH, LH, and prolactin were determined. Already four hours after intramuscular administration of 5 mg estradiol valerate, there was a significant increase in estradiol and estrone, which continued up to 3–5 days. Thereafter, both estrogens fell slowly and continuously; estradiol more pronounced than estrone. The estradiol and estrone curves ran almost synchronously in the logarithmic display. The estrone level was always higher than the estradiol level. In the postmenopause, estrone is the dominant estrogen, regardless of the BMI, even after intramuscular estradiol administration. FSH and LH were significantly suppressed by 60% and 50%, respectively. The prolactin level increased significantly and exceeded the normal range. Hormone replacement therapy (HRT) is preferably carried out orally or transdermally. In individual cases, especially if the exposure to medication is relatively high, HRT can be carried out with intramuscular sex steroids. This form of application is valued due to its independence from daily tablet intake and its good effectiveness. Most therapy recommendations recommend the dose of 10 mg estradiol valerate every 2–3 weeks. On the occasion of a routine estradiol determination, we accidentally found extremely high estradiol levels in a patient, which were over 900 pg/ml. The inquiry revealed that the patient had received 10 mg of estradiol valerate intramuscularly. This finding prompted us to reconsider and review the concept of HRT in postmenopause with intramuscular estradiol applications.

INTRODUCTION

In the postmenopausal period, estrone becomes the dominant estrogen due to the loss of ovarian function. The estradiol produced by conversion from androgens and estrone is, according to the research by von Holst [1], far below the level of estrone. It is known that after oral medication of estradiol in the postmenopausal period, estrone remains dominant [2]. After transdermal estradiol application, however, the gastrointestinal first-pass effect with the initial liver metabolism does not occur. This makes the estradiol level higher than that of estrone. The estradiol-estrone quotient remains > 1 and thus in the physiological range [3]. After intramuscular injection of estradiol, the first-pass effect and metabolism in the liver are primarily bypassed.

As part of the therapy support, we were interested in whether sufficiently high estradiol levels could be achieved after intramuscular administration of 5 mg estradiol valerate and how the estradiol-estrone quotient behaved. In addition, the influence of this dose on the suppression of FSH and LH and the estradiol-induced prolactin secretion were of interest.

MATERIAL AND METHODS

In 17 healthy postmenopausal women aged 56 to 85 years, mean age 67.9 years (Table 1), as part of the therapy monitoring for intramuscular hormone application of 5 mg estradiol valerate (1 amp. Estradiol Depot 5 mg Jenapharm), before, four hours after the application, and then every other day, i.e. on the 3rd, 5th, 7th, 9th and 11th day, blood was taken for the determination of 17β-estradiol, estrone, FSH, LH, and prolactin. The determination of estradiol was carried out with the enzyme immunoassay from Serono (<5 pg/ml, interassay accuracy: 65 pg/ml, CV 16.4%; 210 pg/ml, CV 10%; 490 pg/ml, CV 5.7%), those of estrone with the enzyme immunoassay from DSL (<1 pg/ml, CV 2–4%). FSH (<0.37 IU/l, CV 6%), LH (0.5 IU/l, CV 8%), and prolactin (0.6 ng/ml, CV 4%) were determined with the enzyme immunoassays from Abbott. The blood samples were taken regularly at 11 a.m. The subjects were in the postmenopause for 3–34 years, an average of 17.2 years.

Table 1: Age, body mass index (BMI) and postmenopausal age (PM age) of the patients

	Age	BMI	PM age
B.M.	79	27.0	27
B.C.	72	25.9	10
B.W.	77	29.7	30
F.E.	72	28.3	19
F.S.	67	27.0	16
G.M.	64	25.8	14
H.M.	59	29.2	11
K.B.	64	26.5	12
L.I.	75	35.3	25
M.R.	59	23.3	10
R.I.	70	22.6	17
R.M.	57	27.9	9
R.Ge.	71	33.7	17
R.Gi.	56	23.7	3
S.F.	85	27.2	34
T.W.	59	27.1	6
T.E.	68	27.0	32
Mean	67.9	27.5	17.2
Min	56	22.6	3
Max	85	35.3	34

The body mass index (BMI = weight/length²) fluctuated between 22.6 and 35.3 and averaged 27.5 according to the WHO classification in the area of overweight (Table 1). The average BMI of 27.5 corresponds to the age-dependent normal value for postmenopausal women around the age of 70. The mean values and the standard deviation were calculated for the individual parameters. The Wilcoxon rank sum test (non-parametric test for two connected random samples) was used to statistically secure the results. A significance of $p < 0.05$ was used as a basis.

RESULTS

The intramuscular administration of 5 mg of estradiol quickly led to an increase in the estradiol level in the required preventive range and beyond, so that a higher dosage was not necessary.

Estrone and Estradiol

Already four hours after intramuscular administration of 5 mg estradiol valerate, a significant increase in estrone and estradiol was detectable regardless of the BMI (Figures 1–3). This significant increase

continued for both estrogens up to 3–5 days after application. Thereafter, both estrogens fell continuously up to day 11, estrone more slowly than estradiol. On the 11th day after application, the mean estradiol level was still 71 pg/ml. With the logarithmic representation of the mean value curves it could be shown that the levels for estrone and estradiol run almost synchronously (Figure 1). This synchronicity in the course of the curve cannot be clearly demonstrated in the linear representation (Figure 2). The estrone level was higher than the estradiol level in both normal and overweight and obese women (Figure 3). Before the intramuscular estradiol application, the absolute difference in the logarithmic representation between the estrone and estradiol levels was significantly greater than between the 3 and 9 days after the application. With a linear representation, the absolute differences were greatest on the 3rd and 5th day.

Figure 1: Serum concentrations (mean values with 95% confidence interval) of estrone (E1), estradiol (E2) in logarithmic representation before and after the single intramuscular application of 5 mg estradiol valerate

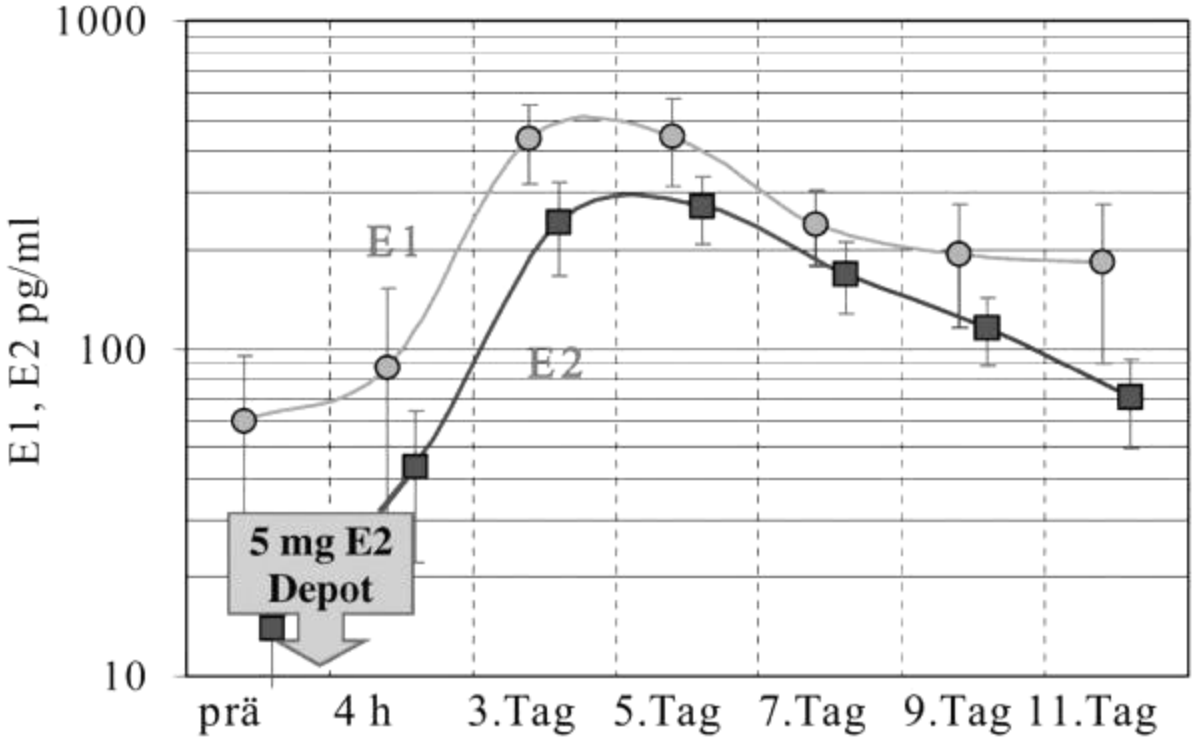


Figure 2: Serum concentrations (mean values with 95% confidence interval) of estrone (E1), estradiol (E2) in a linear representation before and after the single intramuscular application of 5 mg estradiol valerate

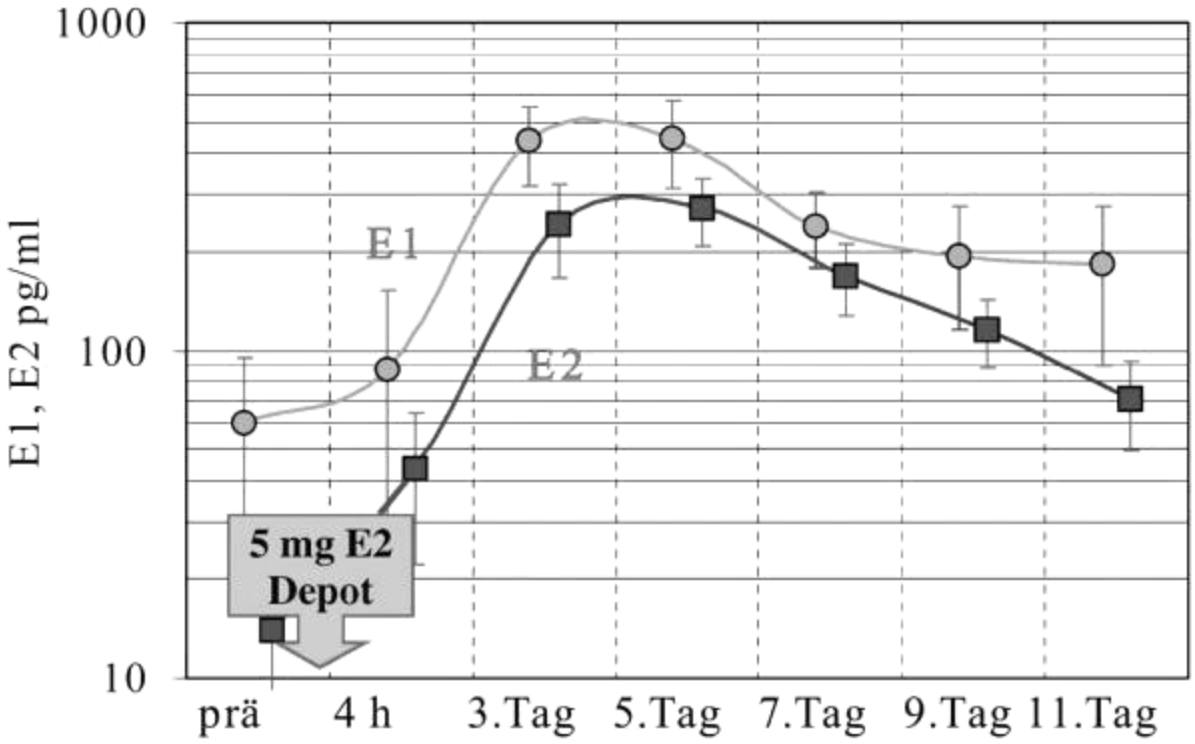


Figure 3: Serum concentrations of estrone (E1) and estradiol (E2) before and after the single intramuscular application of 5 mg estradiol valerate in four case studies

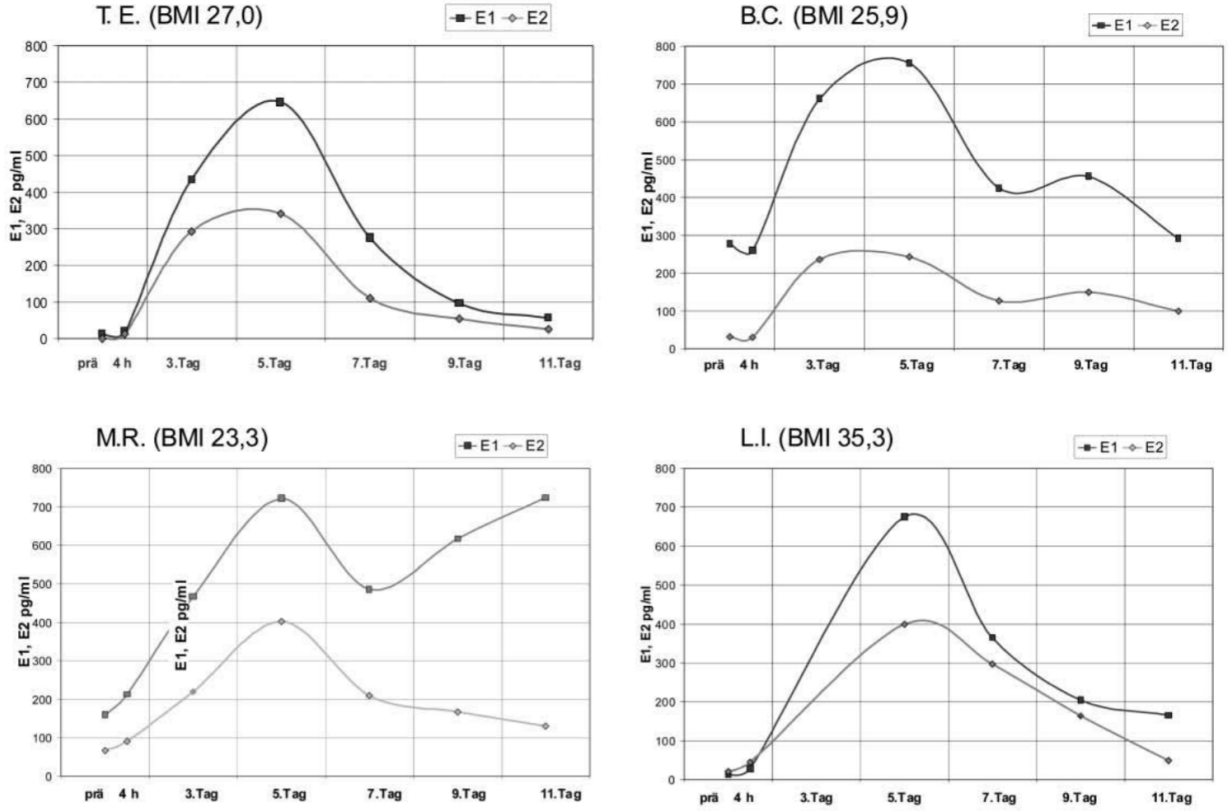


Table 2: Mean values for estrone (E1), estradiol (E2), FSH, LH, prolactin (PROL), and the E1/E2 quotients during the individual examination times: before administration and 4 hours as well as 3, 5, 7, 9, or 11 days after administration of 5 mg estradiol valerate intramuscularly

	Before	**4 hours**	**3rd day**	**5th day**	**7th day**	**9th day**	**11th day**
E1 (pg/ml)	59.7 (± 35.5)	87.0 (± 66.1)	437 (± 121)	447 (± 134)	242 (± 63)	195 (± 79)	183 (± 93)
E2 (pg/ml)	14.0 (± 9.0)	43.4 (± 21.2)	244 (± 77)	272 (± 62)	169 (± 42)	115 (± 27)	71.0 (± 21.7)
FSH (IU/l)	48.8 (± 9.8)	48.0 (± 11.7)	24.9 (± 3.6)	20.1 (± 4.0)	21.6 (± 4.7)	19.1 (± 5.0)	18.5 (± 5.2)
LH (IU/l)	25.2 (± 6.7)	24.8 (± 3.4)	12.5 (± 3.6)	18.6 (± 6.5)	18.9 (± 4.8)	15.5 (± 4.3)	13.0 (± 4.2)
PROL (ng/ml)	8.30 (± 4.34)	7.77 (± 1.81)	23.0 (± 11.8)	27.5 (± 9.2)	30.1 (± 10.0)	27.5 (± 11.8)	24.4 (± 10.8)
E1/E2	4.26	2.01	1.79	1.65	1.43	1.69	2.59

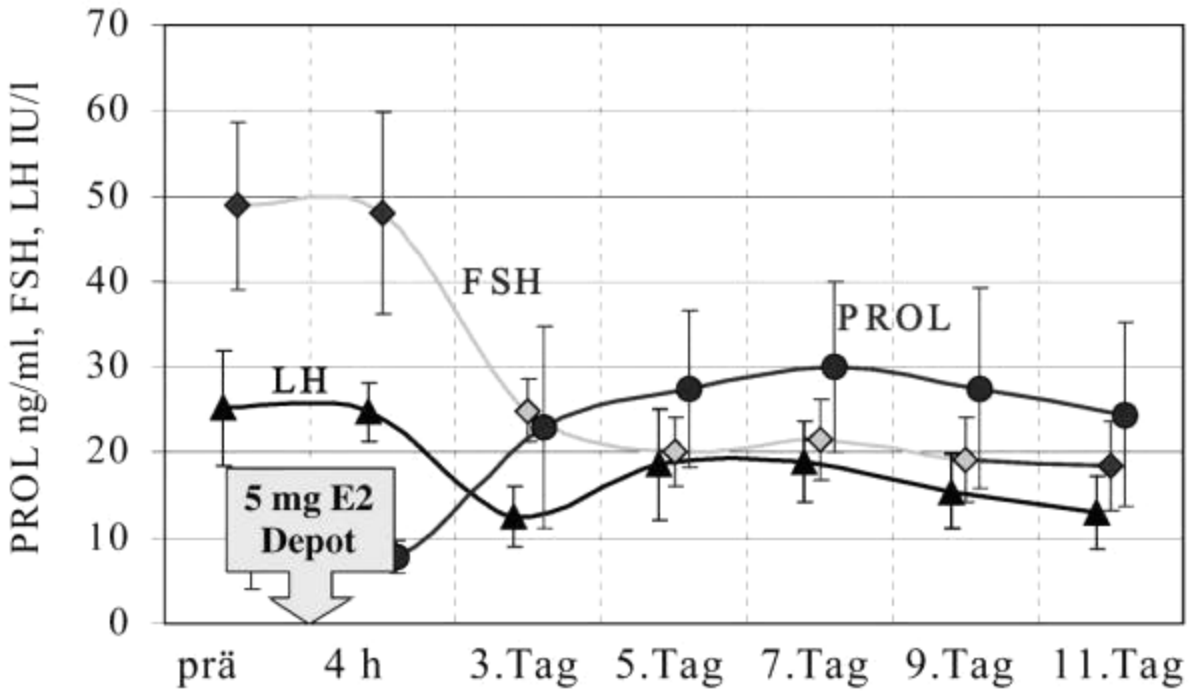
E1-E2 Quotient

The estrone-estradiol quotient averaged 2.2 and ranged between 4.26 and 1.4 on the individual days of the examination. The estrone-estradiol quotient decreased four hours after the application from 4.26 before the estradiol administration to 2.0 and then fell to 1.4 by the 7th day, and then rose again as the estradiol level continued to fall. On day 11 the quotient was 2.59.

FSH and LH

After intramuscular administration of 5 mg estradiol valerate, both FSH and LH were suppressed compared to the previous values. FSH fell significantly by day 11 to 38% of the initial value. The LH level was also significantly inhibited. The maximum inhibition after 11 days was 48% (Figure 4). The reductions for FSH and LH were significant between days 3 and 11.

Figure 4: Serum concentrations (mean values with 95% confidence interval) of FSH, LH, and prolactin (Prol) before and after the single intramuscular application of 5 mg estradiol valerate



Prolactin

After the application of 5 mg estradiol valerate, prolactin increased significantly. From the 3rd day on, the normal range was exceeded (Figure 4). However, there were considerable individual and inter-individual fluctuations.

DISCUSSION

5 mg of estradiol valerate administered intramuscularly lead to an increase in estradiol, which is well above the range reported by reproductive women. Düsterberg et al. [4], who in their study administered 4 mg estradiol intramuscularly to two ovariectomized postmenopausal women and observed increased estradiol levels after 12 days, we found estradiol values of 71 pg/ml 11 days after injection of 5 mg. These levels were still well above the basal values. Oriowo et al. [5] reported that 9 women between 25 and 30 years of age who had been pretreated with a hormonal contraceptive for 3 months had their basal values again 7–8 days after application of 5 mg of estradiol valerate. The maximum of the estradiol and estrone levels was registered after 2–3 days. The estrone values were lower than the estradiol values at all times of the examination. In agreement with the findings obtained by Oriowo et al. [5] in sexually mature women, the opinion so far has been that after intramuscular administration of estradiol valerate, the estrone-estradiol quotient is similar to that which dominates estradiol during sexual maturity. In contrast, we found that in the postmenopausal period, estrone remains the dominant estrogen even after intramuscular administration of estradiol. Only the ratio of estrone to estradiol shifts. The estrone-estradiol quotient becomes smaller, but always remains > 1. The estrone level in normal, overweight, and obese postmenopausal women after intramuscular administration of estradiol is almost parallel to the estradiol level and increases its dominance with the falling estradiol level. The differences between the findings of Oriowo et al. [5] and our results are probably due to the different study arrangements. Oriowo et al. (1980) administered estradiol intramuscularly to women in the reproductive phase whose ovarian function had been partially suppressed by hormonal contraceptives. In this phase of life, however, the basal ovarian

function was maintained despite the use of hormonal contraceptives, and primordial follicles were continuously recruited. In contrast, our investigations were carried out on women with an average age of 67.9 years, who had already been in postmenopause for at least 3 years and whose ovarian function had ceased. According to the studies by Panotopoulos et al. [6], the BMI in Great Britain, Germany, France, and Italy increases from the age of 20 to 60 from 21 to 25.5. The BMI of 27.5 therefore roughly corresponds to the normal distribution in the phase of life around the age of 70. The changes we have described could be due to a change in the balance of 17β-hydroxysteroid dehydrogenase activity in the postmenopause in favor of estrone, if sufficient estradiol is available.

CONCLUSIONS

With the presented investigations it could be shown that after intramuscular administration of 5 mg estradiol valerate sufficiently high estradiol levels are achieved. The higher doses of 10 mg estradiol intramuscularly recommended in the literature for hormone replacement therapy are not required. In the postmenopause, estrone remains the dominant estrogen even after intramuscular administration of estradiol.

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