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Continuous low dose estradiol released from a vaginal ring versus estriol vaginal cream for urogenital atrophy

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Abstract

Objectives: To determine if the efficacy of continuous low dose estradiol released from a vaginal ring is equivalent to estriol vaginal cream regarding improvement of the patient's subjective feeling of vaginal dryness and to determine if there is a preference for either of the two study treatments. *Methods:* Open-label randomized parallel group trial with active control with a blind evaluation of vaginal cytology and with a cross-over (change-over) phase for preference comparison. One hundred and sixty five postmenopausal women with symptoms of vaginal dryness and signs of vaginal atrophy were randomized to an estradiol ring (Estring®) or estriol cream (Synapause®). The duration of each treatment period was 12 weeks. *Results:* Both study treatments were equally effective regarding the ability to alleviate the symptom feeling of vaginal dryness and the signs of vaginal atrophy. Both treatments were efficient in restoring the vaginal mucosa, recorded as higher maturation values and as decreased vaginal pH. Estring was superior to estriol cream regarding preference of treatment. Both treatments were equivalent for the occurrence of adverse events, including bleeding. *Conclusion:* data from this change-over study confirm efficacy and safety of both the vaginal ring and cream in the treatment of postmenopausal women with urogenital atrophy symptoms and signs. The patients had a strong preference for the vaginal ring. Copyright © 1997 Elsevier Science Ireland Ltd.

Keywords: Urogenital atrophy; Estradiol ring; Estriol cream; Vaginal mucosa

1. Introduction

Estrogen replacement therapy is justified in postmenopausal women with complaints of hot flushes and severe sweating and with symptoms of urogenital atrophy, including the feeling of vaginal dryness [1]. For treatment of urogenital symptoms, local therapy by administration of estrogens in vaginal pessaries, creams or tablets has been found more appropriate than oral or parenteral administration forms, thereby avoiding enterohepatic circulation, inactivation by hepatic metabolism and unwanted systemic effects. For successful local therapy a low dose of estrogens (estriol, estradiol, conjugated estrogens) is sufficient [2–4] without eliciting a proliferative endometrium. However, these administration forms might not always be practical because of irregular application intervals, bolus absorption, low absorption capacity of the fat-based vehicle and stickiness. To circumvent these problems a vaginal ring has been developed with a continuous low dose release of estradiol during 3 months [5,6].

During the use of this vaginal ring systemic levels of estradiol are very low (about 30 pmol/l) [5,6].

The primary objective of this study was to determine if the efficacy of treatment of atrophic vaginal mucosa in postmenopausal women is equivalent for the estradiol ring and estriol cream regarding improvement in the subjective symptom of vaginal dryness and if there is a patient's preference for either of the two administration forms. The secondary objective was to deter-

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mine if the two treatments are equivalent regarding improvement in objective symptoms of vaginal atrophy (vaginal cytology), improvement in subjective symptoms of vaginal atrophy other than vaginal dryness (urgency, dysuria etc.), improvement in vaginal mucosa appearance according to doctor's assessment, and ability to decrease vaginal pH, and to determine if the two treatments are different regarding acceptability.

2. Subjects and methods

2.1. Study design

The study was performed with a randomized, open label, cross-over (change-over) design with efficacy comparison between study treatment (estradiol releasing vaginal ring) and an active control after the first treatment period and an evaluation of treatment preference after the second period.

The study was performed in accordance with rules laid down in the Declaration of Helsinki. The protocol was approved by the Ethics committees of the participating hospitals. Before inclusion to the study, the women gave their written informed consent. The study was performed at 12 centres. Patients were allocated to one of two treatment schedules via a central randomization list.

2.2. Subjects

Patients were eligible to participate in the study if they were at least 2 years after spontaneous or surgical (bilateral oophorectomy) menopause and having both symptoms and signs of atrophic vaginitis, including the feeling of vaginal dryness. Excluded were women with known contra-indications or precautions for estrogen therapy and women with sex hormone treatment during the last 3 months.

2.3. Medication

The study product was a silicon vaginal ring of core design (an estradiol loaded core, containing 2 mg micronized 17β-estradiol) with a constant release of ≈ 7.5 μg estradiol/24 h for 90 days (Estring®, Pharmacia Uppsala, Sweden). The control product was an estriol vaginal cream (Synapause®, Nourypharma Oss, The Netherlands) containing 1 mg estriol/g of cream. The dosage used was 0.5 mg daily for the first 2 weeks followed by a maintenance dose of 0.5 mg three times weekly. This control drug was chosen because Synapause is the most commonly used drug for this indication in The Netherlands.

After randomization, the patients were treated either with the estradiol-releasing vaginal ring or the estriol vaginal cream for 12 weeks (i.e. 3 months). At the check-up visit after 3 months, the patients were changed to the alternative treatment for the next 3-month treatment period.

2.4. Efficacy assessments

The patient's subjective symptoms of vaginal atrophy were assessed at inclusion and at the check-up visit after 3 months of treatment. The patient was specifically asked to rate the following symptoms: feeling of vaginal dryness, pruritus vulvae, dysuria, urinary urgency and dyspareunia. The severity ratings were defined as mild (awareness of symptom or sign, but easily tolerated), moderate (enough to interfere with usual activities of daily living) or severe (incapacity to work or carry out activities of daily living). The gynaecological inspection included the investigator's visual assessment of the appearance of vaginal mucosa. At inclusion, signs of estrogen deficiency-derived atrophic vaginitis were confirmed by the investigator, taking into account the presence or absence of pallor, petechiae, friability and vaginal dryness. The recordings were repeated at the check-up visit after 3 months of treatment. Severity ratings were defined as above. Specific questions regarding treatment acceptability were asked at the visit at 3 months including a rating of her overall opinion of the treatment received during this period as excellent, good, acceptable, bad or unacceptable. At the 24-week visit the patient was asked to express her preference for the ring or the cream.

The objective symptoms of vaginal atrophy were assessed by performing a vaginal cytology at inclusion and after 3 months. Vaginal smears were obtained with the Cytobrush® (Medscand AB, Malmö, Sweden) sampling technique from the upper third of the right lateral vaginal wall [7]. All smears were analysed by an independent cytopathologist, blinded with regard to pretreatment/treatment, to duration of treatment, to current treatment alternative and to patient identity. The numbers of parabasal, intermediate and superficial cells out of 100 cells (maturation index) were counted twice and a mean maturation index (MI) was given for each sample. For further evaluation the maturation value (MV) was calculated from the MI by multiplying the percentages of the cell types by the following factors: 0.2 for parabasal cells, 0.6 for intermediate cells and 1.0 for superficial cells [8].

In connection with the gynaecological examination, measurement of the vaginal pH was performed at inclusion and at the visit after 3 months of treatment by the use of a pH indicator strip (Spezialindikator, Merck, Darmstadt, Germany) attached to the wall of the proximal third of the vaginal vault for at least 1 min and thereafter evaluated according to the instructions on the package.

2.5. Statistics

All data listings, tabulation and statistical analysis were performed using the SAS-system, version 6.07 [9,10].

All randomized patients who actually started the first treatment period were included in an intention-to-treat (ITT) analysis of efficacy and acceptability. A per-protocol (PP) analysis was performed for patients who reasonably adhered to all protocol conditions.

The sample size calculation resulted in a need to include 170 patients in the study and was based on the proportion of patients improved or free of symptom (i.e. responders) at the 3-month visit for the patient's feeling of vaginal dryness, and on the following: the proportion was previously estimated to be, on average, 80% for the two treatment sequences based on experience from recent studies. For a significance level of 5% (per one-sided test), a power of 80%, an equivalence interval from -20 to 20% units, the number of patients required was estimated to be 69 per treatment sequence, i.e. 138 for the entire study. After compensating for patients not valid for the efficacy analysis (withdrawals/dropouts), the final sample size was chosen to be 170 patients.

Demographic and prognostic variables at baseline were checked for homogeneity between the two treatment sequences.

For variables registered on a nominal scale, the testing was performed using a χ^2 test for independence while variables registered on an ordinal scale were tested for unequal distributions using Wilcoxon's two-sample test. An analysis of variance (ANOVA) model was used for variables registered at least on an interval scale.

Confidence intervals were calculated where appropriate; in the equivalence situation 90% confidence intervals were used, elsewhere 95%. The statistical tests were one-sided in the equivalence tests; elsewhere two-sided tests were used. No adjustment for multiplicity was performed, but exact P-values are presented for each test.

Equivalence was analyzed with a confidence interval [11] corresponding to a 'two one-sided alpha-test'.

The hypotheses were:

H_0:Population parameter (ring) > Population parameter (cream) $+\theta$

H_0:Population parameter (ring) < Population parameter (cream) $-\theta$

If both these hypotheses were rejected at the 5% level, corresponding to the 90% confidence interval completely being covered by the equivalence interval $(-\theta, \theta)$, equivalence was shown.For all variables evaluated as rates, θ has been set to 20 percentage units, whereas θ was set to 5 units for MV and to 0.5 for vaginal pH.Non-equivalence results have been followed by a nominal 95% confidence interval for the difference in improvement (test for 0-difference), to be interpreted in a descriptive manner.

The variables measuring a subjective symptom or sign were analyzed for the proportion of patients with the initial symptom or sign and at least improving for each variable respectively. The method for analysing the treatment preference between Estring and Synapause was based on the single proportion technique [12].

For the opinion on administration form (registered on a five-grade scale), Wilcoxon's two sample test was used for comparing distributions at week 12. Further, the proportions of patients giving the answer 'good' or 'excellent' were compared using the technique for comparing two proportions above.

3. Results

Out of 170 intended, 168 women were randomized to the study and 165 actually started the first treatment period, 83 in the ring-cream sequence and 82 in the cream-ring sequence. In total 27 patients were excluded from per protocol analysis at 12 weeks, 11 treated with the ring, 16 with cream. Another 16 patients were excluded from per protocol analysis at 24 weeks, nine treated in the second period with vaginal cream, seven with the ring. Reasons for exclusion were protocol violations, such as wrong inclusion, interruption of treatment, later visits than allowed, premature withdrawal from treatment and miscellaneous reasons. At premature withdrawal from treatment itching, increased eczema or allergic reaction was noted in two ring-, and three cream-treated patients. One patient lost the ring.

The number of patients in the per protocol analysis at 12 weeks for efficacy and acceptability were 72 in the ring-cream sequence, and 66 in the cream-ring sequence and in the PP analysis at 24 weeks for preference 63 (ring-cream group) and 59 (cream-ring group).

Patient characteristics at baseline demonstrated no significant differences between the two sequences (all P-values > 0.20), with a mean age of 57.9 and 58.5 years and a mean time after menopause of 8.5 and 9.4 years.

3.1. Efficacy

Changes of the symptom 'feeling of vaginal dryness' between baseline and the visit at 12 weeks are summarized in Table 1. As this symptom was a prerequisite for inclusion, all women suffered from this symptom at baseline. Equivalence between the treatments was shown.

For the symptom pruritus vulvae, a significant difference in change in favour of the vaginal ring was ob-

Table 1
Patient's assessment of the changes of the symptom 'feeling of vaginal dryness' from baseline to 12 weeks treatment in ITT and PP analysis

Effect	Ring		Cream	
	ITT	PP	ITT	PP
Symptom free	47 (57%)	44 (61%)	43 (52%)	40 (61%)
Improved	21 (25%)	21 (29%)	22 (27%)	15 (23%)
Unchanged	7 (8%)	7 (10%)	10 (12%)	9 (14%)
Worse	0 (0%)	0 (0%)	2 (2%)	2 (3%)
No data	8 (10%)		5 (6%)	
n	83	72	82	66

served in the ITT-analysis. For the symptoms dyspareunia, dysuria and urinary urgency, non-equivalence but no significant difference was shown between the two treatments (Table 2).

Equivalence was stated between the two treatments in the physician's assessment of changes of the appearance of the vaginal mucosa (Table 3).

The quantitative analysis of the vaginal smears showed no difference between the two treatments in the change of the number of parabasal, intermediate and superficial cells. Patients were classified as responders to treatment if the level of parabasal cells decreased more than 25% in comparison with baseline. At 12 weeks, 84% of the patients treated with the ring responded and 85% in the cream-treated group. The MV increased from 46 (mean; S.D., 15) to 71 (S.D., 9) with the ring and from 47 (S.D., 16) to 70 (S.D., 8) with the cream in the ITT-analysis. Also in the PP-analysis, equivalence with no significant difference in MV was shown between the two groups.

Vaginal pH decreased from 6.7 (S.D., 1.3) to 5.3 (S.D., 1.0) with the vaginal ring and from 6.4 (S.D., 1.3) to 5.2 (S.D., 0.9) with the cream. Between groups, these differences in changes in the ITT- and in the PP-analyses showed non-equivalence with nonsignificant difference.

3.2. Acceptability, opinion on the administration form

At the 12-week visit, 39 (47%) of the 83 patients randomized to be treated with the vaginal ring in the first period gave the opinion 'excellent' on the administration form as compared with five (6%) of the 82 patients during treatment with the vaginal cream (Fig. 1). Seventy eight percent of patients treated with the ring answered 'good' or 'excellent' as compared with 40% in the cream-treated group. This difference is significant with a P value of less than 0.0001 (95% CI: 22–54). A test on the registered five-graded scale leads to P of less than 0.001.

3.3. Preference

In the ITT-analysis, 106 patients (64%) out of the 165 entering the trial preferred treatment with the ring explicitly (Table 4, Fig. 2). The other patients preferred cream (29 patients, 18%), or had no preference (eight patients, 5%). For 22 patients (13%) no data was available. The 95% confidence limit for the ring preference ranges from 56 to 71%, i.e. significantly different from

Table 2
Percent of patients with initial signs cured and improved between baseline and 12 weeks of treatment (responder rate). Patient's assessment of subjective symptoms

Symptom	Ring		Cream		Equivalence (90% confidence interval)	Significance of difference
	Cured (%)	Improved (%)	Cured (%)	Improved (%)		
2a: Intention to treat analysis						
Vaginal dryness	57	25	52	27	Yes (−9 to 14)	
Pruritus vulvae	63	20	55	5	No (6 to 42)	$P = 0.03$
Dyspareunia	50	18	53	27	No (−26 to 3)	NS, $P = 0.22$
Dysuria	70	0	60	10	No (−28 to 27)	NS, $P = 0.76$
Urinary urgency	57	18	46	26	No (−34 to 7)	NS, $P = 0.3$
2b: Per protocol analysis						
Vaginal dryness	61	29	61	23	Yes (−4 to 18)	
Pruritus vulvae	65	19	63	3	No (−3 to 37)	NS, $P = 0.18$
Dyspareunia	65	26	65	25	Yes (−11 to 14)	
Dysuria	73	0	56	13	No (−26 to 34)	NS, $P = 0.92$
Urinary urgency	41	18	47	25	No (−35 to 9)	NS, $P = 0.39$

NS, nonsignificant.

Table 3
Physicians assessment of vaginal mucosa, change between baseline and 12 weeks of treatment in patients with initial signs

Symptom	Free of sign (%)		Equivalence (90% confidence interval)	Significance of difference
	Ring	Cream		
3a: Intention to treat analysis				
Pallor	72	65	no (−8 to 23)	NS, $P = 0.49$
Petechiae	80	81	yes (−17 to 14)	
Friability	81	82	yes (−14 to 11)	
Dryness	80	77	yes (−10 to 16)	
Atrophy	52	52	yes (−15 to 13)	
3b: Per protocol analysis				
Pallor	77	71	no (−9 to 22)	NS, $P = 0.57$
Petechiae	85	82	yes (−13 to 19)	
Friability	88	88	yes (−12 to 13)	
Dryness	89	86	yes (−10 to 14)	
Atrophy	57	59	yes (−17 to 13)	

NS, non significant.

our null hypothesis of equal preference (50% for each treatment), with a P of less than 0.0004. In a PP-analysis, including only those PP-patients stating a preference, 81% out of 116 patients preferred the vaginal ring (95% CI, 72–87%, $P < 0.0001$).

3.4. Safety

Both study treatments were well tolerated. No difference was seen in the number of patients having (minor) vaginal irritation at inspection between treatment groups at baseline, or at 12 or 24 weeks, but the incidence of irritation reported at baseline was remarkably reduced after treatment with either of the study drugs at 12 weeks ($P = 0.04$). The decrease from baseline to 12 weeks was maintained at 24 weeks.

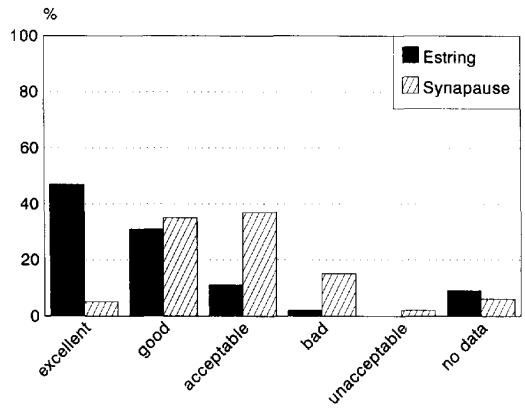

Fig. 1. Distribution of the percentage of patients stating their opinion on received treatment expressed at 12 weeks (ITT analysis).

3.5. Adverse events

The frequency and kind of adverse events were the same in both treatments. Four serious adverse events were reported in the study, two during use of the ring and two during vaginal cream. One patient experienced pruritus and urticaria 4 days after ring insertion. After removal of the ring the symptoms disappeared. Causality with the study drug was assessed as possible. Another woman had mild rectal bleeding 62 days after insertion of the ring (157 days after inclusion in the study). Bleeding was reported to be caused by aspirin taken for headache. Causality with the study drug was assessed as unlikely. Treatment with the ring was continued. One woman reported mild vaginal bleeding during 6 days starting 1 day after inclusion to the study, treated with vaginal cream. Five days later itching started and continued for 57 days. Treatment with vaginal cream was discontinued on day 16. Causality with study drug was not assessed. Another patient had severe bleeding due to endometrial hyperplasia starting

Table 4
Distribution of patient's preference for study treatment at the end of the study after use of both study treatments

Treatment preference	Ring-cream sequence		Cream-ring sequence	
	ITT	PP	ITT	PP
Vaginal ring	56 (67%)	48 (76%)	50 (61%)	46 (78%)
Vaginal cream	13 (16%)	13 (21%)	16 (20%)	9 (15%)
No preference	3 (4%)	2 (3%)	5 (6%)	4 (7%)
No data	11 (13%)		11 (13%)	
n	83	63	82	59

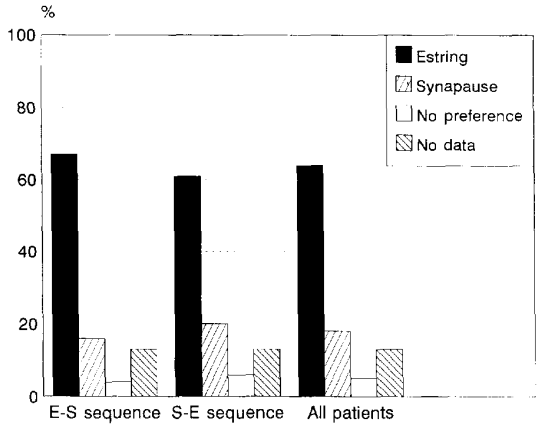

Fig. 2. Results for stated preference presented as percentage of patients preferring Estring, Synapause or had no preference at the end of the study (24 weeks, ITT analysis).

50 days after inclusion, treated with vaginal cream in the first period. Causality with study drug was assessed as possible.

Vaginal haemorrhage (bleeding, spotting) was recorded 11 times during the study in ten patients (five during the ring and six during cream treatment). Vaginal origin, including one case of bleeding from an ectropion, was reported for seven bleeding events (three with the ring and four with cream). Unknown origin was reported for one cream-treated patient. The event occurred on the first day of the study and was reported on the visit at 12 weeks. Endometrial origin for bleeding was reported for three bleeding events in the study. One patient treated with the ring was specified after hysteroscopy to be bleeding due to an atrophic endometrium. The other two patients, one treated with cream and one with the ring, both in the cream-ring sequence, showed endometrial hyperplasia with cytological atypia, diagnosed after curettage. Causality with study drug was classified as possible.

4. Discussion

The present study was primarily designed in order to evaluate a possible difference in treatment preference between the two study medications, a recently developed estradiol releasing vaginal ring, and an estriol vaginal cream. The change-over design of the study allows for an evaluation of clinical efficacy and acceptability after the first study period at 12 weeks and for a unique evaluation of treatment preference after the second period at 24 weeks. This is the first controlled, randomized, change-over study evaluating treatment preference for the vaginal ring, in which the two compared treatments were used within one and the same study.

Equivalence was shown between the two treatments in improvement of vaginal dryness, signs of atrophy, vaginal pH and vaginal cytology. Our results are quite similar to those found in two other studies, comparing the ring with another estriol vaginal cream given in a higher dose [13] or with estriol pessaries [14].

The blind evaluation of vaginal cytological smears confirms objectively an effect of similar magnitude on vaginal mucosal maturation by both treatments. The proportions of the different cell types (MI) differ somewhat as compared with other ring studies [13–15], most likely reflecting the fact that the evaluation was performed by different cytopathologists. Our results for estriol treatment were somewhat better than in other studies [13,16], probably as a result of a higher maintenance dose after the first 2 weeks of three times a week instead of two times weekly. The overall efficacy results are well in line with findings in previous ring studies and further confirm the clinical relevance of local estrogen therapy in the treatment of urogenital symptoms and signs.

Strikingly similar effects were demonstrated for both treatments with a greater similarity than in earlier studies comparing the ring with estriol pessaries and creams [13,14], in which usually higher ratings for efficacy were found for the vaginal ring. There are two possible explanations for the closer similarity in our study. Firstly, the already-mentioned higher maintenance dose of the cream of 0.5 mg three times a week. Secondly, estriol cream could have a more favourable effect than estriol pessaries, as was demonstrated by others [17].

Both vaginal MV and pH are established objective assessments of vaginal atrophy and evaluation of estrogen treatment [15]. Factors known to influence vaginal cytology, pH and bacterial flora [18,19], like body mass index, diastolic blood pressure, years since menopause, and smoking habits, were equally distributed among both groups.

In the evaluation of treatment preference between the two study treatments, the ring was clearly the preferred treatment. When evaluating the opinion on the administration form, a highly significant difference was found in favour of the vaginal ring. This advantage in favour of the ring was further enhanced by the highly significant difference in treatment preference. The study design certainly allows for optimal comparison. The patients used both treatments within the same study. Even in the most conservative testing procedure (ITT), tests for difference in treatment preference resulted in a P-value of less than 0.0004. This fact was already indicated in previous studies, and is now confirmed in a study primarily designed for this specific evaluation.

Acceptability and preference are highly important parameters for local vaginal treatment forms, not least due to the fact that urogenital estrogen deficiency symptoms, in contrast to vasomotor symptoms, continue

throughout life and thus call for very long treatment. The excellent acceptance and the strong preference for the vaginal ring are very encouraging regarding compliance with long-term treatment.

During this study, in the ring-cream sequence, three events of bleeding were recorded during treatment with the ring and one with the cream. In the cream-ring sequence, five events of vaginal bleeding were recorded during the use of the cream and two events during the ring.

The incidence of vaginal bleeding is well in accordance with data from previous vaginal ring studies. In pooled Estring data an incidence of 4.3% was found, of which 3.8% were from atrophic endometria or of vaginal origin (Pharmacia AB Sweden, unpublished data). In the controlled studies, 3.8% of the Estring patients reported vaginal bleeding, whilst 2.4% of patients treated with 0.5 mg estriol pessaries, 6.7% with a higher dosage of estriol cream and 7.6% treated with a cream containing conjugated equine estrogens reported vaginal bleeding. In the present study, a relation between the two bleeding events with an endometrial origin (one with the cream and one with the ring) and the study medication is possible, but in our opinion this is unlikely given the very low systemic levels of estradiol with the vaginal ring [5,6]. Our results are in agreement with the advice that concomitant use of progestogens is not necessary with the use of estriol cream, nor with the use of the estradiol releasing vaginal ring.

5. Conclusion

Highly beneficial and clinically important effects were recorded for both Estring and Synapause cream in this study. The excellent effect was not only restricted to vaginal atrophy symptoms and signs, but also to symptoms emanating from the lower urinary tract as dysuria and urgency. Close similarity in both safety and efficacy profiles was observed. The women had a strong preference for the low dose estradiol vaginal ring. The estradiol-releasing vaginal ring is confirmed to be an excellent alternative in the treatment of postmenopausal patients with symptoms and signs of urogenital atrophy.

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References

[1] Kenemans P, Barentsen R, Van de Weijer PHM. Practical HRT. Medicom Europe BV, Bussum, The Netherlands, 1995.

[2] Hage JC, Benedek Jaszmann LJ. A study of the effects of premarin cream in the postmenopausal women. Curr Ther Res 1983; 33: 925–929.

[3] Kicovic PM, Cortes-Prieto J, Milojevic S, Haspels AA, Aljinovic A. The treatment of postmenopausal vaginal atrophy with Ovestin vaginal cream or suppositories: Clinical, endocrinological and safety aspects. Maturitas 1980; 2: 275–282.

[4] Eriksen PS, Rasmussen H. Low-dose 17β-estradiol vaginal tablets in the treatment of atrophic vaginitis: a double-blind placebo controlled study. Eur J Obstet Gynecol Reprod Biol 1992; 44: 137–144.

[5] Holmgren PA, Lindskog M, Von Schoultz B. Vaginal rings for continuous low-dose release of oestradiol in the treatment of urogenital atrophy. Maturitas 1989; 11: 55–63.

[6] Schmidt G, Andersson SB, Nordle Ö, Johansson CJ, Gunnarsson PO. Release of 17-β-oestradiol from a vaginal ring in postmenopausal women: pharmacokinetic evaluation. Gynecol Obstet Invest 1994; 38: 253–260.

[7] Ulmsten U, Stormby N. Evaluation of the urethral mucosa before and after oestrogen treatment in postmenopausal women with a new sampling technique. Gynecol Obstet Invest 1987; 24: 208–211.

[8] Hustin J, Van den Eynde JP. Cytologic evaluation of the effect of various estrogens given in postmenopause. Acta Cytol 1977; 21: 225–228.

[9] SAS Institute Inc, SAS language: Reference, Version 6, 1st edn., Cary, NC:SAS Institute, 1990; 1042 pp.

[10] SAS Institute Inc, SAS/STAT User's Guide, Version 6, 4th edn., Cary, NC:SAS Institute, 1989; 846 pp.

[11] Schuirman DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equi valence of average bioavailability. J Pharmacokinet Biopharm 1987; 15: 657–680.

[12] Fleiss JL. Statistical Methods for Rates and Proportions. Wiley, New York, 1981, 321 pp.

[13] Pigné A. A comparative study of effects of continuous low-dose estradiol released from a vaginal ring versus estriol vaginal cream in postmenopausal women with symptoms and signs of urogenital atrophy. A multicentre study. In: Notelovitz M, ed. Proc 1st International Workshop on Estring. Royal Soc Med Services, London 1993; 51–63.

[14] Henriksson L, Stjernquist M, Boquist L, Alander U, Selinus I. A comparative multicenter study of the effects of continuous

low-dose estradiol release from a new vaginal ring versus estriol vaginal pessaries in postmenopausal women with symptoms and signs of urogenital atrophy. Am J Obstet Gynecol 1994; 171: 624–632.

[15] Smith P, Heimer G, Lindskog M, Ulmsten U. Oestradiol-releasing vaginal ring for treatment of postmenopausal urogenital atrophy. Maturitas 1993; 16: 145–154.

[16] Heimer GM, Englund DE. Effects of vaginally-administered oestriol on postmenopausal urogenital disorders: a cytohor monal study. Maturitas 1992; 14: 171–179.

[17] Mattson LA, Cullberg G. A clinical evaluation of treatment with estriol vaginal cream versus suppository in postmenopausal women. Acta Obstet Gynecol Scand 1983; 62: 397–401.

[18] Milsom I, Arvidsson L, Ekelund P, Molander U, Eriksson O. Factors influencing vaginal cytology, pH and bacterial flora in elderly women. Acta Obstet Gynecol Scand 1993; 72: 286–291.

[19] Nilsson K, Risberg B, Heimer G. The vaginal epithelium in the postmenopause — cytology, histology and pH as methods of assessment. Maturitas 1995; 21: 51–56.