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D. W. Sturdee

LONGTERM INVESTIGATION OF THE ENDOMETRIAL SAFETY OF A NEW SEVEN-DAY SEQUENTIAL OESTRADIOL-LEVONORGESTEL COMBINATION PATCH

INTRODUCTION

In post-menopausal women with an intact uterus, oestrogen therapy alone, unopposed by progestogen is associated with an increased risk of endometrial hyperplasia and cancer [1]. The risk of hyperplasia can be significantly reduced by the concurrent administration of a progestogen for at least 10 days each cycle [2, 3]. There is a wide range of oral replacement therapy (HRT) regimens incorporating oestrogen with cyclical progestogen but there are very few transdermal sequential HRT preparations. Oral oestradiol has to be administered in a high dosage to achieve therapeutically effective plasma levels of oestrogen, because most will be inactivated during the first pass metabolism [4]. Transdermal oestrogen avoids the hepatic first pass effects, is absorbed into the circulation directly and produces plasma levels similar to those in the premenopausal woman with much lower dosage. The transdermal route is becoming increasingly popular and now that the progestogens levonorgestrel (LNG) [5] as well as norethisterone can also be absorbed by a patch, combined HRT regimens administered totally by patch are possible. Most oestradiol patches need to be changed twice per week, but the development of a 7-day patch is even more patient friendly as it might improve compliance. Fixed dose combinations of oestrogen and progestogen are not suitable for every patient, and the choice of dose combination allows greater flexibility in prescribing to cope with individuals who need different dosages to control symptoms or prevent side effects.

The objective of this study was to assess the effect on the endometrium of three different dosages of sequential oestradiol and LNG in a new 7-day transdermal matrix patch.

METHODS

In a randomised, prospective, controlled, open-label, multicentre, multinational (UK, the Netherlands and Germany) study of one year duration, the effects of a transdermal, sequential combined oestradiol/levonorgestrel hormone replacement therapy (HRT) regimen in three dosage was investigated on the endometrium of non-hysterectomised, post-menopausal women.

Treatment consisted of a cyclic combined oestradiol (E2)/levonorgestrel (LNG) regimen in three different dosages:

- a 15 cm^2 matrix patch providing 50 µg E2/day for the first two weeks of the cycle and during the second half of the cycle 50 µg E2/day plus 10 µg LNG/day;
- a 22.5 cm^2 matrix patch delivering 75 µg E2/day for the first two weeks of the cycle and during the second half of the cycle 75 µg E2/day plus 15 µg LNG/day;
- and a 30 cm^2 matrix patch providing 100 µg E2/day for the first two weeks of the cycle and during the second half of the cycle 100 µgE2/ day plus 20 µg LNG/day.

Each patch was applied for 7 days.

The effects on the endometrium were assessed by endometrial biopsy using the Pipelle® sampling or Vabra® suction curette. Biopsies were taken at study entry and at the planned study end (cycle 13) or if the patient withdrew from treatment earlier. Two independent pathologists using international accepted histological evaluation criteria reviewed all biopsies.

RESULTS

A total of 550 women were screened for which 468 were randomised; 156 to the 15 cm^2 patch group, 157 to the 22.5 cm^2 patch group, and 155 to the 30 cm^2 patch group.

The endometrial biopsy results at baseline did not reveal any unsuspected findings or abnormalities. The results of the final biopsies taken at the end of the study or earlier if the patient withdrew are shown in Table 1 summa-

Table 1: Results of the final biopsies

	15 cm^2		22.5 cm^2		30 cm^2		total	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Non-hyperplastic	135	100	134	99.3	128	99.2	397	99.5
Hyperplastic	0	0	1	0.7	1	0.8	2	0.5
Total	**135**	**100**	**135**	**100**	**129**	**100**	**399**	**100**
Upper 95 % CI-limit	**2.20**		**3.47**		**3.63**		**1.57**	

rized in non-hyperplasias or hyperplasias.

There were two cases of endometrial hyperplasia, representing 0.5 % of the evaluable samples (n = 399). The corresponding 95 % upper confidence limit was 1.57 %. There was one case of atypical hyperplasia in the 22.5 cm^2 patch group and one case of simple hyperplasia in the 30 cm^2 treatment group.

The different dosage combinations produced variations in the bleeding response and percentage of patients with no bleeding at all during the whole study decreased dose-dependently. The day of onset of cyclic bleeding was remarkable constant for each dosing group averaging around day 12 –13 from start of the progestogen. The overall patient satisfaction with the bleeding profile was very high.

In general, the patches were tolerated very well and severe skin reactions were in the range of about two percent. There were no differences to be seen which could be related to the patch size.

More than 20.000 patches were assessed with respect to patch adhesiveness and it was to be judged as very good. About 82 % of all patch applications demonstrated sufficient patch adhesiveness. In general, no relevant differences could be detected between the three patch sizes.

Discussion

The primary objective of the study was to investigate the endometrial safety during treatment with three different dosages of new 7-day transdermal oestradiol and LNG regimens. The finding of only two cases of hyperplasia (0.5 %), only one of which had atypia, is reassuring and this percentage is well below the expected incidence rate for hyperplasia during sequential HRT [2, 3], and the background rate in untreated post-menopausal women of around 5 % [6]. All three regimens seem to provide satisfactory protection of the endometrium with the dose of LNG in each regimen balancing the effect of the oestradiol.

Patients taking sequential HRT regimens are counseled to expect regular monthly bleed and this is usually accepted as small price to pay for the benefits of therapy. However, most women would prefer not to bleed if possible, or have a slight bleed. The better bleeding profile with 93 % of the group being satisfied was with the lowest oestradiol dose compared to 77 % satisfaction in the highest dose. This is a further indication for giving patients the lowest dose that is suitable for them. In this study the drop-out rate due to bleeding overall was no higher than in other comparable studies.

Dr. med. David W. Sturdee

David W. Sturdee has been a consultant in obstetrics and gynecology for Solihull Health Authority since 1981 and for Birmingham Heartlands and Solihull NHS Trust since 1995. He is also Honorary Senior Clinical Lecturer at Birmingham University, UK. He qualified in medicine at St. Thomas' Hospital Medical School in London, UK, in 1969, and continued his training until he took up the position of Registrar of General Surgery at Hereford County Hospital in 1973, and then Registrar of Obstetrics and Gynaecology at Birmingham Maternity Hospital and Birmingham and Midlands Hospital for Women. After a period of research as Honorary Research Fellow in the Department of Obstetrics and Gynaecology at the University of Birmingham, he took several Senior Registrar positions in obstetrics and gynecology. He has been involved in menopause research since 1976, with particular interest in hot flushes and the effect of HRT on the endometrium.

Dr. Sturdee is a founder member of the International Menopause Society and past chairman of the British Menopause Society. He is on several editorial boards, and is joint Editor-in-Chief of the official journal of the International Menopause Society, Climacteric. He regularly gives lectures both nationally and internationally on menopause and related subjects.

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The rates of skin irritation and also the patch adhesiveness are in the range of the rates already known from the mono oestradiol patch (Fem® 7).

This study has demonstrated that all three dosages of this new 7-day sequential oestradiol/LNG preparation provide good endometrial protection and a high level of patient satisfaction with the bleeding response. The different dosage combinations provide flexibility in prescribing, so that the dose may be tailored to the individual. This is an important general principle of prescribing and should help with patient satisfaction and continuance.

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