Randomised crossover comparison of skin irritation with two transdermal oestradiol patches

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Transdermal oestradiol patches relieve menopausal symptoms,¹ prevent bone loss,² and cause metabolic and direct vascular changes consistent with a reduced risk of arterial disease.³ They may also cause skin irritation at the site of the patch. The first patches contained an alcohol reservoir, oestradiol being released through a semipermeable membrane held against the skin by a ring of adhesive. Subsequent patches have oestradiol dissolved in the adhesive matrix and distributed across the whole patch. Anecdotal and published reports suggest that matrix patches may cause fewer skin reactions than reservoir patches.^{4 5} We compared the two designs in women with a history of skin irritation at the site of the patch.

Patients, methods, and results

We recruited women requiring oestrogen replacement who had previously discontinued transdermal treatment because of skin reactions. Those with active dermatological disease or using non-inhaled corticosteroids were excluded. Women were randomised to receive either a matrix patch (Evorel) or a reservoir patch (Estraderm TTS), then the other patch, each for eight weeks at a dose of 50 µg/24 h. Patches were applied according to the manufacturers' instructions and changed twice weekly. Women with an intact uterus also received progestogen.

Women who experienced unacceptable skin irritation could discontinue the current treatment at any time. Those stopping the first treatment progressed immediately to the second; those discontinuing the second treatment left the study. At each change of patch women recorded the degree of local redness, swelling, and itching on a diary card. A standardised clinical photograph of the most recent patch site was taken at the end of each phase. Computerised digital analysis of these photographs will be reported separately.

Eighty two women were recruited. Twelve had previously used a matrix patch (all Evorel) and 70 had used a reservoir patch (58 Estraderm, 12 Estracombi). Seventy two women completed the study, of whom nine discontinued both patches because of skin irritation and 30 discontinued one patch. Of this second group, significantly more women discontinued the reservoir patch (26) than the matrix patch (four) ($P < 0.001$ (McNemar's test); table 1). Sixty nine women

returned completed diary cards, of whom 41 recorded a moderate or severe reaction to only one type of patch—35 to the reservoir patch, six to the matrix patch ($P < 0.001$). Seventeen women reported reactions to both patches and 11 to neither.

Comment

Previous comparative studies have concentrated on assessing the efficacy of reservoir and matrix patches rather than determining local skin reactions.^{4 5} So far as we know this is the first study to use a crossover design and recruit only those women who had previously discontinued patches because of skin irritation. Though most women in this study had previously discontinued a reservoir patch, the crossover design reduced the influence of selection bias. Similar results were seen in women who had previously stopped a matrix patch (table 1). The likelihood of discontinuation was not significantly affected by the order of the patches ($P > 0.05$; binomial test), ruling out a significant carryover effect of treatment. This suggests that contact dermatitis is the most likely mechanism for skin irritation to oestradiol patches.

Over half of the women who had previously experienced a severe skin reaction to oestradiol patches (predominantly reservoir patches) did so again when rechallenged. Skin reactions causing discontinuation of treatment were much less common with the matrix patch than the reservoir patch. If women have stopped using reservoir patches because of a skin reaction, then a trial with a matrix patch is worth while. The risk of a similarly severe reaction is less than one in five compared with more than one in two if the reservoir patch is tried again. Further studies are required to investigate whether there are differences in local skin reactions to the numerous matrix patches which have now become available.

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Table 1 Numbers of women discontinuing each patch because of skin irritation

	Discontinued neither	Discontinued reservoir patch only	Discontinued matrix patch only	Discontinued both	Total
Matrix patch first	18	12	0	5	35
Reservoir patch first	15	14	4	4	37
Total (%)	33 (46)	26 (36)	4 (6)	9 (13)	72 (100)
Subgroup who had previously discontinued a matrix patch	3	2	1	3	9