

25 mg oestradiol implants—the dosage of first choice for subcutaneous oestrogen replacement therapy?

ABSTRACT

Objective To assess the oestrogen concentrations and symptom relief obtained with 25 mg oestradiol implants.

Design Open, observational study.

Subjects Twelve symptomatic, post-menopausal women seen in a designated menopause clinic.

Intervention A 25 mg oestradiol pellet was inserted subcutaneously, blood samples were obtained before implantation and at regular intervals (2-4 weeks) until symptoms were refused as hypoestrogenaemia developed.

Main outcome measures Change in symptom score following implant treatment. Concentrations of oestrogens and their metabolites before and during low dose subcutaneous oestradiol therapy.

Results Ten of the 12 women had excellent symptom relief, associated with oestradiol concentrations in the follicular range for between 28 and 35 weeks. The ratio of circulating oestrogen metabolites remained physiological, despite the oestradiol concentrations being substantially higher on treatment.

Conclusions We suggest that 25 mg pellets should be used as the initial dose for subcutaneous oestrogen treatment, and a combination of return of symptoms and weeks since insertion used to judge the timing of reimplantation.

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In the United Kingdom there are nearly ten million postmenopausal women (Office of Population Censuses and Surveys 1990) and the use of hormone replacement therapy is increasing in this group as more women recognize that symptoms due to oestrogen deficiency can easily be treated. The oral route of administration of oestrogens is cheap and provides effective therapy for climacteric problems, but because relatively large doses of oral oestrogens are required to produce plasma oestradiol concentrations within the physiological range, adverse symptoms and detrimental hepatic effects may result (Cooke *et al.* 1975; Geola *et al.* 1980; Helgason 1982; Lobo 1980; Notebohm 1987; Von Schulz 1988). Percutaneous and subcutaneous methods of administration avoid these high portal vein concentrations and are thus considered safer in certain circumstances, for example in women with a past history of hepatic or clotting dysfunction. The most commonly used oestradiol implants are 50 mg and 100 mg and these, particularly with repeated usage, may lead to supraphysiological concentrations, a source of anxiety and potential side effects (Barlow *et al.* 1986; Barlow 1988; Eden 1988; Ganger *et al.* 1989; Swyer 1989). On the principle of prescribing the lowest dose of a drug necessary for appropriate symptom relief, we wished to investigate the efficacy and duration of action of the lower dose 25 mg oestradiol implant.

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Subjects and methods

Twelve symptomatic, postmenopausal women were recruited for this open, observational study, from new referrals to a designated menopause clinic. Twelve symptomatic, post-menopausal women seen in a designated menopause clinic.

The profile of plasma oestrogen metabolites varies with the route of administration, for example, after gut absorption the subsequent hepatic breakdown results in a disproportionate rise in oestrone and oestrone sulphate (Selby *et al.* 1989). As there are no published data on the metabolic profiles associated with the subcutaneous route of administration, we wished to study the concentrations of oestrone, oestradiol and their glucuronides and sulphates after implant therapy.

weeks since insertion used to judge the timing of reimplantation.

trations and symptom scores. Wilcoxon's signed rank test was performed on the paired results of pre- and post-implant oestrogen (and metabolites) concentrations.

Results

All the women had an increase in serum oestradiol concentrations and relief of symptoms by 2 weeks after implantation. One woman was withdrawn from the study at 20 weeks because she developed symptoms from a benign brain tumour. Another woman required reimplantation after 16 weeks because of the return of symptoms in the presence of low serum oestradiol concentrations, but the other 10 women continued in the study for a median of 29 weeks (range 28–35) after implantation.

The change in symptom score over time in all 12 women is shown in Fig. 1. Symptoms decreased in all the women within the first 2 weeks. The median reduction in symptom score was 60%. Excluding the women who required another implant after 16 weeks and the woman with the brain tumour, further treatment was not required until at least 26 weeks after implantation (median 29 weeks, range 26–35 weeks).

The change in serum oestradiol concentrations during the treatment period is shown in Fig. 2. By 2 weeks after implantation, the median serum oestradiol concentration was 377 pmol/l, with a four fold variation between the highest and the lowest concentrations (190–782 pmol/l). After 3 months the intersubject variation had narrowed and oestradiol concentrations remained at early to mid follicular phase levels until the end of the study. Analyzing the 'area under the curve' for the oestradiol concentrations over the period of the study, the results are all within the physiological range (Fig. 3), and with less intersubject variation (approximately 2.5 fold).

There was no correlation between oestradiol concentrations and symptom relief in the overall group (data not shown). Rapid return of symptoms, associated with a decrease in the oestradiol concentration to 175 pmol/l, was noted in one woman at 14 weeks. In the other women the return of symptoms was associated with higher oestradiol concentrations than their initial values (range 340–182 pmol/l) and no threshold level could be defined.

Oestradiol concentrations exceeded oestron concentrations

At entry into the study the women completed a modified 'Kupperman' questionnaire (Kupperman *et al.* 1953)—an 11 point self-assessment symptom questionnaire. The symptoms enquired about included hot flushes, numbness or tingling in the hands or feet, difficulty sleeping, nervousness and sadness, dizziness and tiredness, headaches and pains in the joints or muscles, palpitations and formation. The women scored the severity of their symptoms from 0–3 corresponding to 'not at all', 'mild', 'moderate' or 'severe' with weighting of four-fold for the severity of the hot flushes and two-fold for the subsequent three symptoms. The maximum possible score was thus 51.

A 25 mg oestradiol pellet was inserted subcutaneously, under local anaesthesia, in the buttock or lower abdomen (Greenblatt *et al.* 1949; Thom & Studd 1980). The implant used was the standard fused crystalline 17 β -oestradiol preparation, 2.2 mm in diameter (Organon Laboratories, Cambridge, UK). Because of the small size of the implant, and thus the small size of the trocar, a suture was not required. All women were given oral dydrogesterone (Duphasion, Duphar Laboratories, Southampton, UK), 10 mg daily, for 12 days, from the first day of the calendar month.

The Kupperman questionnaire was completed and blood sample was obtained baseline, 2 weeks and 4 weeks after the treatment and then every 4 weeks until 20 weeks after the treatment, or sooner, if symptoms returned. Subsequently, the women were seen every 2 weeks until they completed the study. The blood was spun and the serum stored at -20°C. The study was completed when symptoms recurred, as assessed by a substantial increase in the symptom score, or when the E_2 concentrations returned into the menopausal range. The serum was analyzed for oestron, oestradiol and oestrone and their sulphate and glucuronide conjugates as described previously (Selby *et al.* 1989). The intra-assay variations ranged from 9.1 to 15.8%.

Data presentation

The serum concentrations and symptom scores are presented as medians and individual results, as the data were not normally distributed and the numbers were small (Gardner & Altman 1989). The week of implantation was designated week 0 and the symptom scores during the study were expressed as a percentage of the initial score, due to the wide variation between the women. In the figures, the data are grouped into 2-, 4- and then 2-week intervals. The 'area under the curve' for the oestradiol concentrations over time is presented for the 10 women who continued after 15 weeks (Mathews *et al.* 1990).

Statistical analysis

Linear regression analysis was performed on the E_2 concen-

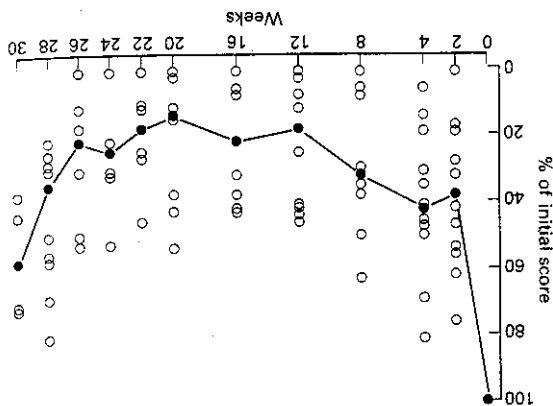


Fig. 1. Change in symptom score following 25 mg oestradiol implantation at week 0. Results are shown as a percentage of the initial (pre-implantation) score. —●—, median; ○, individual.

oestradiol implants has been clearly demonstrated, although larger studies to corroborate these results would be valuable. The fact that 10 of the 11 women, who were able to complete the study, had symptom relief for over 6 months confirms that use of this implant dose is realistic. The oestradiol concentrations achieved were within the early follicular range in most women, although there was considerable variation between women. This suggests that the higher concentrations achieved with the 50 mg and 100 mg implants are unnecessary for control of symptoms. The variation between individuals was greater in the first 3 months than subsequently, being four to five fold between the lowest and the highest. Taking the whole period of the study, however, there was less intersubject variability in oestradiol concentrations, as represented by the 'areas under the curve'. We were unable to establish the reasons for the intersubject differences, as the oestrogen profiles did not show any consistent patterns that could be associated with altered absorption or metabolism; neither could these differences be explained by variation in body mass index.

In practice, however, the differences in circulating oestradiol concentrations with this dose of implant were narrow compared with those seen after oral administration, where five to ten fold variations are seen (Akporhoro & Forchuck 1980), and also showed less variation than with the 50 or 100 mg pellets (Thom *et al.* 1981). With these higher doses of implants there is a greater differential between peak and trough values and a declining mean value in the months following implantation. This is clinically important as falling concentrations seem to provoke symptom return (Thom & Studd 1980; Barlow 1988; Cardozo *et al.* 1984). This has been described as tachyphylaxis but this is probably not an appropriate example of that phenomenon. Tachyphylaxis usually describes a reduced physiological response to a standard dose of drug. In the situation found with high dose oestradiol implants, however, the problem is the return of symptoms in the presence of supraphysiological concentrations of oestrogen. This may be due to a relative change in oestradiol concentrations, or to decreases below a threshold level. We did not find this problem with the 25 mg dose.

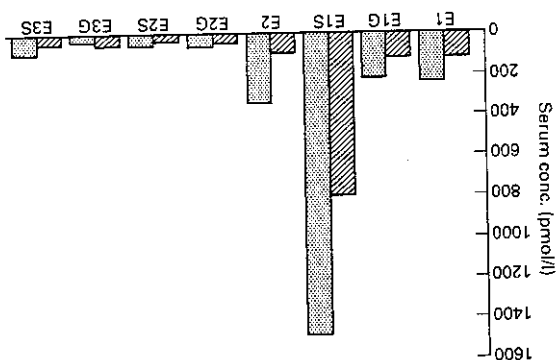
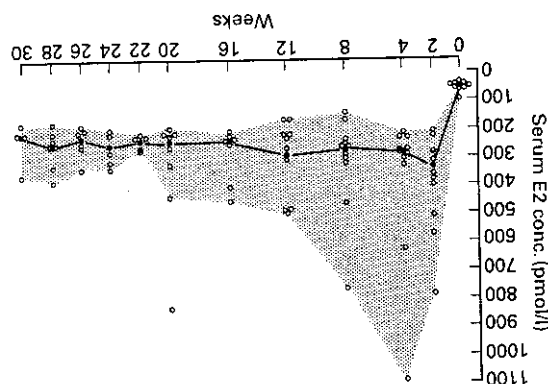


Fig. 2. Serum oestradiol (E₂) concentrations following 25 mg E₂ implantation at week 0. The shaded area highlights the range (excluding one result at week 20-21). ●, median.



In this group of 12 unselected women the efficacy of low dose

Discussion

in all women after treatment, with the oestradiol/oestrogen ratio reversing from a median of 0.56 at baseline to 1.5 at 2 weeks and thereafter. Fig. 4 demonstrates the changes in the various oestrogen metabolites 8 weeks after the 25 mg oestradiol implant. Before treatment, oestrogen sulphate concentrations predominated with very low concentrations of the other oestrogens fractions. At 8 weeks after implantation the median concentrations of oestradiol and all the metabolites (except oestradiol glucuronide) had risen substantially but the ratios were similar to pre-treatment. The main metabolite, oestrogen sulphate, was still in the highest concentration in the serum, but the oestradiol concentration was disproportionately higher.

We were, however, unable to correlate the return of symptoms with serum oestradiol concentrations. Despite maintaining concentrations well above pretreatment values until the end of the study, all women eventually complained of worsening of symptoms. Whether this was an effect of the aforementioned change in the concentrations of oestradiol, or one of the other metabolites, could not be established. Return of symptoms was not an accurate guide to absolute oestradiol concentrations, but using a 25 mg implant the women were unlikely to develop very high concentrations with repeated implants. We suggest, therefore, that the timing of reimplantation be judged by a combination of symptom recurrence and time since insertion. If, however, rapid return of symptoms were to occur, measurement of oestradiol concentration could differentiate between symptom return due to hypoeostrogenaemia and that adequate (or high) oestradiol concentrations, where reimplantation may be inappropriate.

We have demonstrated that the absorption of E_2 from the subcutaneous site of implantation leads to a more physiological profile of circulating oestrogens than that seen with oral administration, and similar to that seen with the transdermal route of absorption (Selby *et al.* 1989). The implant does, however, avoid the inconvenience of twice weekly change of patches and the development of adverse skin reactions. Although there are no data suggesting that altered ratios of the metabolites are deleterious *per se*, the very high concentrations of oestrone sulphate seen with oral administration may be detrimental avoided.

The main indication for hormone replacement therapy is symptom relief. This dose is effective. It may be that supra-physiological replacement will be important in certain situations; for example the augmentation of bone density in established osteoporosis, but this is unlikely to be needed for the majority of women. Savvas *et al.* (1988) have suggested that where low concentrations of oestrogen replacement are provided orally, bone mineralization may not be preserved. A 'threshold level' has not, however, been established and when treating prophylactically repeated bone densitometry may be needed to confirm the individual effect rather than a population effect. Preliminary studies on the oestradiol patches suggest that E_2 concentrations similar to those found in this study may be adequate to maintain bone mass (Stevenson *et al.* 1990), and Nolevitz *et al.* (1987) found no change in bone mineral density in the radius of six women using the 25 mg implant.

The risk to the endometrium of unopposed oestrogens is not lessened because the woman delays her next implant. Progesterogens must be administered to all women with an intact uterus and should be continued until the oestradiol concentrations fall within the menopausal range of until there are no further withdrawal bleeds. We used dydrogesterone because it is a non-androgenic progestogen that is also effective in producing secretory change in the endometrium (Siddle *et al.* 1990). The use of 25 mg implants as treatment for menopausal symptoms of many women could be easily managed by their general practitioner, with the minimum of equipment, and very little risk of overdosing. The oestradiol concentrations remain in the physiological range in many women for far longer than was appreciated previously.

We have demonstrated that the efficacy and duration of action of the 25 mg implant is greater than was commonly

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