UNALTED BASAL PROLACTIN SECRETION DURING SHORT-TERM OESTRIOL TREATMENT IN POST-MENPAUSAL WOMEN*

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SUMMARY

Six post-menopausal women were submitted, at 1 month interval, to oral oestriol treatment for 14-day periods at daily doses of 2 and 6 mg. Blood samples were collected for LH, FSH and PRL measurements (by RIA) every other day during treatments as well as during a 14-day control period. Though the effect on LH levels was questionable, oestriol resulted in a clear and significant, although moderate, gradual decrease of mean FSH levels. At the doses used, which are effective in the treatment of menopausal symptoms, but are devoid of any proliferative effect upon the endometrium, oestriol failed to induce any stimulatory effect on basal PRL secretion in these post-menopausal women.

Decades ago, clinicians suggested that post-menopausal women should be given adequate oestrogen replacement therapy (Wilson & Wilson, 1963). The most favoured argument for such long-term treatment lies in its ability to decrease the age-related bone loss and therefore prevent osteoporosis (Lindsay et al., 1976; Recker et al., 1977). Recent studies (Marshall & Nordin, 1977) suggested that the treatment of choice in post-menopausal osteoporosis might be to use oestrogens with vitamin D3 and calcium supplements. In these studies, ethinyl-oestradiol was used at a daily dose of 25 μg, a dose known to increase circulating PRL concentrations in post-menopausal women (Robyn & Vekemans, 1976).

As recently reviewed (Schoemaker et al., 1977), it is now well established that such oestrogen treatment increases the risk of endometrial carcinoma while it can not be definitively established whether it might increase the incidence of breast tumours, as an excessive risk of breast cancer has been recently reported (Hoover et al., 1976) to be associated with use of conjugated oestrogens, especially after 10 years of treatment. Therefore, the use of oestradiol, which does not induce any endometrial proliferation (Lauritzen & Velibese, 1961; Lauritzen, 1973), might be preferred. Based on studies of uterine growth in immature rats (Hisaw, 1959), oestradiol had been considered as an ‘impeded’ oestrogen. Although oestradiol

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and oestriol were shown to be of equal potency in stimulating all early uterotrophic responses, oestriol failed to stimulate true uterine growth, as evaluated by the increase in dry weight 24 h after administration (Anderson et al., 1975): this differential effect of oestradiol and oestriol was attributed to a difference in the long-term nuclear retention of the oestrogen-receptor complex (Anderson et al., 1975). However, it has been shown on the contrary that oestradiol and oestriol had equal uterine growth-promoting and vascular effects in mature sheep (Clewell et al., 1977).

Nevertheless, oestriol treatment can be used with satisfactory results on hot flushes and vaginal atrophy (Lauritzen, 1973; Lauritzen & Velibese, 1961). At daily doses of 8 mg, it proved to reduce urinary excretion of hydroxyproline (Katz & Kappas, 1968); similarly, the administration of daily doses of 6 and 8 mg oestriol dihemisuccinate induced a significant decrease of the urinary calcium excretion (Gallagher & Nordin, 1975). Furthermore, oestriol succinate, at daily doses of 2 to 8 mg, failed to exhibit any major effect on coagulation function (Toy et al., 1978).

The present study was undertaken to investigate whether oestriol treatment sufficient to suppress menopausal symptoms would induce any stimulation of PRL secretion. Indeed, oestrogens stimulate PRL secretion in the human as well as in animals, depending on the type of oestrogen, on its dose and on the previous hormonal balance (L'Hermite et al., 1972; Robyn & Vekemans, 1976; Robyn et al., 1976).

MATERIAL AND METHODS

Six volunteer women, aged 51-60 years (3-20 years post-menopausal) were treated with oestriol (Aucifemine®; Aaiiphar, Belgium) at daily oral doses of 2 and 6 mg. Each treatment period lasted for 14 days and an interval of at least 1 month separated the two treatment periods. Three women started with the 2 mg dosage and the others with the 6 mg regimen, the drug being administered once daily at 20.00 h. Blood samples were collected between 10.00 h and 14.00 h every other day during treatment as well as during a 14-day control period preceding any drug administration; blood samples were also obtained daily for the 3 days following each treatment period. Care had been taken that the volunteers did not receive oestrogens, nor drugs known to alter PRL secretion, within 6 months prior to the experiment.

All blood samples from the same subject were analysed within the same assay for the serum LH, FSH and PRL concentrations; double-antibody nonequilibrium procedures were utilized for RIAs, as previously described (L'Hermite & Midgley, 1971; Robyn et al., 1971). LH and FSH levels were expressed as mIU/ml by reference to the 2nd international reference preparation of HMG, although LER-907 was used as a standard in the FSH assay. PRL levels were expressed as µU/ml by reference to the pituitary standard 71/222 distributed by the MRC (Division of Biological Standards and Control, Holly Hill, London, England). Human reagents (antisera and purified preparations for labelling) for RIAs of FSH and PRL (VLS no. 3 kit) were kindly donated by the NIAMDD (NIH, Bethesda, Md, USA). A pool of sera from lactating women was utilized as laboratory standard in the PRL assay. Statistical evaluation was performed, after logarithmic transformation, by analysis of variance (using the variance ratio F) according to Snedecor & Cochran (1967).
RESULTS

Mean LH, FSH and PRL levels during the control and the treatment periods are shown in Fig. 1. Treatment with either dose of oestriol failed to result in any statistically significant modification of the overall mean PRL levels, as compared with those recorded during the control period.

During the administration of 2 mg (but not 6 mg) oestriol, mean LH levels were slightly but significantly \((F = 13.6; \ P < 0.001)\) elevated over those of the control period. There appeared however not to be any gradual change in LH levels with continuation of treatment with 2 mg oestriol; no significant modification of mean LH levels occurred after stopping this treatment.

![Graph showing LH, FSH, and PRL levels](image)

Fig. 1. Mean (± SEM) serum concentrations of PRL (in μU/ml by reference to the MRC standard 71/222), LH and FSH (in mIU/ml by reference to the 2nd IRP of HMG) in six post-menopausal women during a control 14-day period (on the left) and two 14-day periods of treatment with oestriol at daily oral doses of 2 and 6 mg. For FSH, the asterisks indicate the levels of statistical significance at each point during and immediately following treatment, as compared with mean FSH levels on the first day of treatment.

During each period of oestriol administration, mean FSH levels declined gradually: although this decline was of slight amplitude, it was quite statistically significant (Fig. 1). Mean FSH levels were significantly decreased during 2 mg \((F = 5.4; \ P < 0.05)\) as well as during 6 mg \((F = 37.2; \ P < 0.001)\) oestriol administration. Moreover, this decrease of FSH was greater with 6 mg than with 2 mg \((F = 14.2; \ P < 0.001)\). FSH levels remained depressed during the 3 days following cessation of each treatment \((F = 17.3 \text{ and } 103.0, \text{ respectively}; \ P < 0.001)\).
DISCUSSION

Although mean overall LH levels during treatment with 2 mg oestriol were significantly greater than control levels, the significance of this finding appears to be questionable in view of the absence of a gradual effect with treatment. It is possible that it might be an artefact, for example related to the wide-amplitude of LH oscillations reported in post-menopausal women (Medina et al., 1976). On the contrary, oestriol treatment led to a clear and progressive, although slight, decrease in mean FSH levels. This finding clearly demonstrated a negative feedback effect, at the hypothalamo-pituitary level, of oestriol, although it had been previously considered as an 'impeded' oestrogen (Hisaw, 1959). In post-menopausal women, an inhibitory effect on FSH but not yet on LH when giving low doses (i.e. 20 μg daily of ethinyloestradiol) of oestrogen has also been reported by Franchimont et al. (1972).

The present data showed also that oestriol treatment—at the daily doses used—failed to induce any increase in basal PRL levels despite slight inhibition of FSH release. Such a lack of stimulatory effect on basal PRL levels has been similarly reported in a very limited study in which post-menopausal women were given the usual doses of 'natural' or conjugated oestrogen (Lind et al., 1978). This is in contrast with use of ethinyloestradiol which has been found to increase basal PRL levels already when a daily oral dose of 25 μg was administered in post-menopausal women (Robyn & Vekezans, 1976); on the other hand, a daily oral dose of 50 μg ethinyloestradiol was found to be devoid of any stimulatory effect on PRL secretion in normally cycling women (Robyn et al., 1976). Thus the present data support our earlier assumption (L'Hermite et al., 1972) that oestrogenic steroids would influence PRL secretion in the human differently, according to the dose, the route of administration, the type of oestrogenic preparation and to the prior hormonal balance of the subjects.

As recently reviewed (L'Hermite et al., 1977), the administration of oestrogens can induce the development of pituitary PRL-producing adenomas in the rat and possibly in the human. Therefore it seemed important to assess whether oestriol treatment, that might become widely used in the near future, would have any PRL-promoting effect in post-menopausal women. Although the present short-term study in a limited number of subjects suggests the absence of such an effect, it remains to be confirmed in a greater number of patients treated chronically.

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Oestriol treatment effect on prolactin


