THE EFFECT OF LONG-TERM MESTRANOL ADMINISTRATION ON CALCIUM AND PHOSPHORUS HOMEOSTASIS IN OOPHORECTOMIZED WOMEN

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SUMMARY

1. A group of women who had undergone hysterectomy and bilateral salpingo-oophorectomy were studied and subsequently given either 20–40 μg of mestranol per day or a placebo for 1 year.

2. The administration of mestranol to these oophorectomized women for 1 year was associated with significant falls in serum calcium and phosphorus concentrations, a fall in urinary calcium excretion and a rise in relative urinary phosphorus excretion.

3. It is suggested that these results are consistent with an increase in sensitivity to calcitonin and that the relative hyperphosphaturia reflects a compensatory rise in parathyroid hormone activity.

The female menopause is accompanied by a significant fall in bone mineral content (Albright, Smith & Richardson, 1941). The way in which the hormonal changes at the menopause influence this progressive loss of bone remains controversial. The part played by oestrogen replacement therapy at the menopause or after oophorectomy in the prevention or treatment of ‘menopausal osteoporosis’ is far from clear (Albright, 1947; Wallach & Henneman, 1959; Jasani, Nordin, Smith & Swanson, 1965). It has clearly been documented that in middle-aged women the serum calcium and phosphorus and urinary calcium excretion can be lowered within a few days by the administration of oestrogens (Young, Jasani, Smith & Nordin, 1968).

Since these oestrogen-induced changes have been offered as a rationale for oestrogen therapy in the prevention and treatment of ‘menopausal osteoporosis’, we were interested to know if prolonged administration of the hormone had the same effect. We report here our findings after the long-term administration of the oestrogen, mestranol, to a group of oophorectomized women.

MATERIALS AND METHODS

Thirty-two women aged 44–58 years who had 3 years previously undergone hysterectomy and...
bilateral salpingo-oophorectomy for non-malignant disease were invited to attend a special clinic. The letter sent to them clearly delineated the tests which would be performed if they came. These women attended the clinic voluntarily and subsequently agreed to re-attend for follow-up purposes, knowing that they were to be given a drug which it was hoped might prevent the development of osteoporosis. These oophorectomized women were then randomly divided into two equal groups. The first was given oral mestranol in a dose of 20–40 µg/day; the second group received similar tablets which contained no active drug (placebo group).

A fasting sample of blood and a specimen of urine collected between 7 and 9 a.m. was obtained at their first attendance. This was repeated after 1 year’s treatment had been completed.

The following tests were performed on the blood and urine obtained. Serum calcium and urinary calcium (U_{Ca}) was measured by using an atomic absorption spectrophotometer as described by Trudeau & Freier (1967). Serum phosphorus (S_{P}) and urinary phosphorus (U_{P}) were determined by using a standard AutoAnalyzer procedure (Method N-4). Serum creatinine (S_{cr}) and urinary creatinine (U_{cr}) were measured by the alkaline picrate method as modified for the AutoAnalyzer (Method N-11b).

From the values obtained for serum and urinary phosphorus and creatinine, the Index of Phosphate Excretion (I.P.E.) was calculated, as described by Nordin & Bulusu (1968), where

\[
I.P.E. = \frac{U_{P} \times S_{cr}}{U_{cr}} - \frac{S_{P} - 2.5}{2}
\]

From the results of urinary calcium and serum and urinary creatinine, a value for calcium excretion (Ca_{E}) was obtained, where

\[
Ca_{E} = \left[\left(U_{Ca} \times S_{cr}\right)/U_{cr}\right] \text{mg of Ca/100 ml of glomerular filtrate (G.F.) (Nordin, Hodgkinson & Peacock, 1967)}.
\]

The statistical method employed was Student’s t test.

**RESULTS**

Table 1 shows that after observation for 1 year the oophorectomized women who had received mestranol had significantly lower mean serum calcium concentrations at 9.54 mg/100 ml than the women who had received the placebo preparation, where the corresponding value was 9.99 mg/100 ml (P<0.01). These changes were accompanied by a significantly lower Ca_{E} at 0.055 mg of Ca/100 ml of G.F. in the former as compared with 0.093 mg of Ca/100 ml of G.F. in the latter (P<0.02). There was also a very significantly lower mean serum phosphorus concentration at 2.98 mg/100 ml in the mestranol-treated women as compared with a mean value of 3.67 mg/100 ml in the placebo group (P<0.001). The mean I.P.E. was significantly higher at +0.122 in the mestranol group in contrast with a value of −0.130 in the placebo group (P<0.02).

The pre- and post-mestranol treatment results were similar to those seen in the mestranol and placebo group after 1 year’s observation (Table 1).

None of the patients in this study developed venous thrombo-embolism; mestranol administration was not associated with such side effects in a much larger group of women under study (Aitken & Hart, 1971).
**Mestranol therapy after oophorectomy**

**Table 1.** The effect of prolonged mestranol and placebo therapy on two groups of oophorectomized women

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>Mean age (years) (range)</th>
<th>Serum calcium (mg/100 ml) (mean ± SEM)</th>
<th>Serum phosphorus (mg/100 ml) (mean ± SEM)</th>
<th>I.P.E. (mean ± SEM)</th>
<th>Ca₈ (mg of Ca/100 ml % G.F.) (mean ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mestranol group</strong></td>
<td>16</td>
<td>49 (45–52)</td>
<td>9.54 (±0.07)</td>
<td>2.98 (±0.11)</td>
<td>+0.122 (±0.058)</td>
<td>0.055 (±0.011)</td>
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<tr>
<td>after treatment</td>
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<td>for 1 year</td>
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<tr>
<td><strong>Placebo group</strong></td>
<td>16</td>
<td>50 (44–58)</td>
<td>9.99 (±0.13)</td>
<td>3.67 (±0.15)</td>
<td>-0.130 (±0.076)</td>
<td>0.093 (±0.010)</td>
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<td>for 1 year</td>
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<tr>
<td><strong>Statistics</strong></td>
<td>t = 3.05</td>
<td>t = 3.72</td>
<td>t = 2.64</td>
<td>t = 2.54</td>
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<td></td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.02</td>
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<tr>
<td><strong>Mestranol group</strong></td>
<td>9.85 (±0.08)</td>
<td>3.63</td>
<td>-0.215</td>
<td>0.094</td>
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<td>before treatment</td>
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<td>after treatment</td>
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<td>for 1 year</td>
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<tr>
<td><strong>Statistics</strong></td>
<td>t = 2.98</td>
<td>t = 4.11</td>
<td>t = 3.66</td>
<td>t = 2.37</td>
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<td>P &lt; 0.01</td>
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**DISCUSSION**

Our findings with regard to changes in serum calcium and phosphorus after oestrogen therapy are similar to those demonstrated by Young *et al.* (1968). In contrast, however, we have clearly shown a quite significant rise in relative urinary phosphorus excretion after prolonged mestranol therapy.

Nassim, Saville & Mulligan (1956) showed in a heterogenous group of five selected subjects that stilboestrol given in a dose of 1 mg/day for 2–3 weeks was followed by a decrease in renal tubular reabsorption of phosphate. They suggested that this effect might be due to a fall in growth-hormone activity.

Ranney (1959) showed an antagonistic effect between oestrone and parathyroid hormone with regard to bone accretion in adult male mice. Jasani *et al.* (1965) suggested that oestrogens produced their effects on calcium and phosphorus homeostasis by antagonizing the action of parathyroid hormone on bone. The subsequent failure of Young *et al.* (1968) to demonstrate changes in relative urinary phosphorus excretion in post-menopausal women after the short-term administration of ethinyl oestradiol at a dose of 200 μg/day appeared to lend weight to this hypothesis. However, the increased relative urinary phosphorus excretion that we have demonstrated in oophorectomized women after prolonged mestranol therapy suggests that parathyroid hormone activity had actually increased and that mestranol had not antagonized the action of parathyroid hormone on the kidney.

In view of the well-established hypocalcaemic hypophosphataemic effect of calcitonin
(Hirsch, Voelkel & Munson, 1964) it would seem reasonable to postulate that oestrogens produce their effects on calcium and phosphorus homeostasis primarily by an associated increase in calcitonin activity. To support this view, Hinde & Phillippo (1968) showed that oophorectomized rats given oestrogens became more sensitive to the hypocalcaemic effect of calcitonin than control animals not receiving oestrogens. Increased calcitonin activity would not explain the rise in relative urinary phosphorus excretion since this is not observed after calcitonin administration in thyroparathyroidectomized dogs (Pak, Ruskin & Casper, 1969), although in intact patients with hypercalcaemia such a phosphaturic effect has been observed after therapeutic doses of calcitonin (Cochran, Peacock, Sachs & Nordin, 1970). It is suggested that the significant hypocalcaemia seen in our patients was sufficient to induce an increase in parathyroid hormone activity and hence bring about an increase in relative urinary phosphorus excretion.

ACKNOWLEDGMENTS

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REFERENCES