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# An Endocrine and Pharmacokinetic Study of Four Oral Doses of Formestane in Postmenopausal Breast Cancer Patients

**M. Dowsett, A. Mehta, N. King, I.E. Smith, T.J. Powles, R.C. Stein and R.C. Coombes**

**43 postmenopausal breast cancer patients were treated orally with the aromatase inhibitor formestane (4-hydroxyandrostenedione) at daily doses of 62.5, 125, 250 or 500 mg for 4 weeks followed by 250 mg daily for a further 4 weeks. For some patients, 62.5 mg did not suppress serum oestradiol levels maximally. The doses of 250 and 500 mg did not differ in their effectiveness. Oestrone levels were suppressed by all doses of formestane but no consistent changes of aldosterone, cortisol or 17-hydroxyprogesterone occurred. Serum levels of sex hormone binding globulin fell by about 15% during treatment with 250 mg formestane reflecting its minor androgenic activity. The maximum concentration and area under the curve of serum formestane levels after the first dose varied in an approximately linear manner with dose. It is concluded that formestane is an effective, specific suppressant of oestradiol levels via the oral route requiring no more than 250 mg to be given daily.**
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## INTRODUCTION

AROMATASE IS a cytochrome $P_{450}$-mediated enzyme complex which converts the androgens androstenedione and testosterone to oestrone and oestradiol, respectively. As such it is a pivotal enzyme in reproductive endocrinology and its manipulation provides a means by which a variety of sex steroid-dependent physiological and pathological processes may be altered. The possibility of treating oestrogen-dependent breast cancer with aromatase inhibitors to reduce the level of the patient's synthesis of oestrogen has been recognised for many years [1]. Aminoglutethimide was the first compound with which this approach was shown to be clinically effective [2–4]. However, aminoglutethimide has a number of clinically significant side-effects and it inhibits a number of other steroid hydroxylases, which necessitates its combination with glucocorticoid for maximum efficacy [5] and therapeutic safety [6]. There has therefore been a widespread search for an aromatase inhibitor which lacks this detrimental characteristic.

Formestane (4-hydroxyandrostenedione) was the first com-

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pound to be used clinically which was specifically selected for use as an aromatase inhibitor [1, 7]. In a series of studies we have demonstrated that formestane is clinically and endocrinologically effective by both the oral and parenteral routes [8–11]. The optimal therapeutic regime for parenteral use has been selected as 250 mg intramuscularly every 2 weeks [11]. The optimal regime for the more convenient oral route remains to be established. When formestane was given orally there was no significant difference in its suppression of plasma oestradiol levels by 250 mg given once, twice or four times daily [11]. In that study the only significant endocrine side-effect noted was a decrease in sex hormone-binding globulin (SHBG) levels which probably reflects a slight androgenic activity of formestane.

The primary aim of the current study was to define the minimal oral dose of formestane to achieve maximally suppressed plasma oestradiol levels. Four oral doses (62.5, 125, 250, and 500 mg once daily) were compared between patients for a period of 4 weeks (part 1). Thereafter all patients switched to a standard dosage of 250 mg once daily to allow a within-patient comparison of doses (part 2). Seconday aims were to determine the effect of these different doses on other endocrine parameters, including SHBG, and to conduct pharmacokinetic analyses after the first dose of formestane.

## PATIENTS AND METHODS

After giving verbal informed consent to the study 43 postmenopausal patients with advanced breast cancer were randomised to receive one of four different doses of formestane orally once daily for 28 days (part 1): 62.5 mg (group A, $n = 12$), 125 mg (group B, $n = 10$), 250 mg (group C, $n = 11$), 500 mg (group D, $n = 10$). From day 28 all patients were treated with 250 mg once daily (part 2). The formestane was provided by Ciba Geigy as sterile microcrystalline powder in vials of 62.5 mg or 250 mg and was stored at 4°C. The powder was suspended in 5 ml of physiological saline per vial before oral administration. For the 125 and 500 mg doses two vials of 62.5 and 250 mg were administered, respectively. All patients had ceased any previous endocrine treatment at least 4 weeks before entry to this study, and no concurrent endocrine therapy was given during the study. Postmenopausal status was defined as >2 years since last menstrual period. Patients were not excluded on the basis of abnormal biochemical renal or liver function tests.

The first dose of formestane was given at 9 am on day 0. Blood samples were taken on days −3, 0 (before the dose), 3, 7, 14, 21, 28 (before the change to the 250 mg dose), 35, 42, 49 and 56. Additional blood samples for pharmacokinetic analysis were taken from 22 patients (6 on 62.5 mg, 5 on 125 mg, 5 on 250 mg and 6 on 500 mg) at the following times after the first dose: 10, 20, 40 min; 1, 1.5, 2, 3, 4, 6, 8 and 12 h. The blood was allowed to clot and the resultant serum was stored at −20°C until analysis. All urine passed between 09.00 on day 0 and 09.00 on day 1 was collected from patients (3 on 62.5 mg, 3 on 125 mg, 4 on 250 mg and 4 on 500 mg) into separate containers for the time points 09.00 to 13.00, 13.00 to 17.00, 17.00 to 21.00 and 21.00 to 09.00. The volume of the urine was measured and a 10 ml aliquot was stored at −20°C until analysis.

Oestradiol [10], aldosterone [12], cortisol [3], 17-hydroxyprogesterone (17-OHP) [13], dehydroepiandrosterone sulphate (DHAS) [13], luteinising hormone (LH) [14], follicle-stimulating hormone (FSH) [14], SHBG [15] and formestane [10] in the serum samples and formestane glucuronide [11] in the urine samples were measured by immunoassays. Serum levels of oestrone were measured by gas chromatography/mass spectrometry (GCMS) [10]. Oestradiol was measured in all samples. Aldosterone, cortisol, LH, FSH and SHBG were measured on days −3, 0, 14, 28, 42 and 56. For oestrone, 17-OHP and DHAS, measurements were made only on samples from days 0 and 28. For those parameters in which values were derived on days −3 and 0, the mean of these values was used as the pretreatment value. This was to achieve a more stable reference point. For each parameter all samples from the same patient were analysed in the same assay batch.

*Table 1. Demographic data for each of the dosage groups*

| Dose formestane (mg) | Age (years) | TSD (years) | Weight (kg) | Height (cm) |
|---|---|---|---|---|
| 62.5 | 65 (41–81) | 3 (0–10) | 56.3 (41.2–96.0) | 164 (154–165) |
| 125 | 65 (51–83) | 6 (0–25) | 57.0 (52.0–74.5) | 165 (143–173) |
| 250 | 70 (50–85) | 2 (0–25) | 61.5 (47.0–69.5) | 153 (143–160) |
| 500 | 67 (51–91) | 4 (0–11) | 59.0 (45.0–78.1) | 158 (150–169) |

Median (range).
TSD = time since diagnosis.

The area under the formestane concentration/time curve (AUC) was determined using the linear trapezoidal rule, and the results were measured to the last measured time point at which formestane was detected (up to 12 h). The elimination rate constant (ERC) was determined for each patient using the section of the concentration/time curve following the point of maximal concentration to 12 h postdosing. The apparent half-life was then calculated as equal to (0.692/ERC) h.

*Statistics*

For all parameters the data approximated to a logarithmic distribution. They are therefore shown as geometric means and 95% confidence intervals. Statistical comparisons were made using the repeated measures design analysis of variance, which for two group comparisons is equivalent to the paired $t$ test. For oestradiol the comparisons were made between pretreatment levels and the mean levels for days 7–28 and days 35–56 for each patient. For aldosterone, cortisol, LH, FSH and SHBG the on-treatment comparisons were made between the mean levels calculated for days 14 and 28 and days 42 and 56. When no blood sample was available for day 56 the value for day 49 was incorporated instead. The data for aldosterone from 5 patients was excluded from statistical analysis because these patients were taking diuretics. 2 of these patients were from group B, 2 from group D and 1 from group A.

## RESULTS

*Patients' characteristics*

The median age, weight and height of the patient population were 67 years, 57.9 kg and 160 cm, respectively. The median time since diagnosis was 3 years. These demographic data are given for the individual dosage groups in Table 1. The 250 mg dose group were the oldest, heaviest and shortest of the four groups. After 4 weeks' treatment, 1 patient on the 125 mg dose and 1 on the 500 mg dose were withdrawn because of progressive disease.

*Hormone changes*

The suppression of serum oestradiol levels during the 56-day treatment period is shown for individual patients in Fig. 1 and

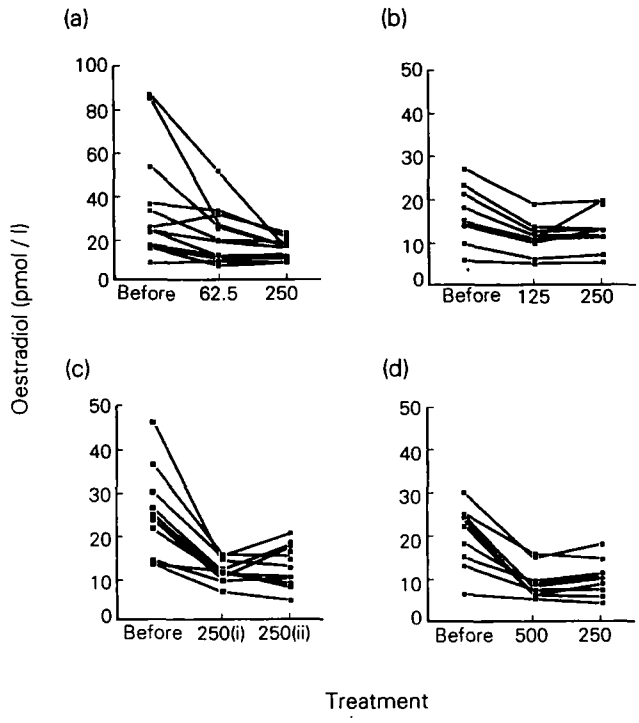


**Fig. 1. Individual serum levels of oestradiol before and during treatment of postmenopausal breast cancer patients with oral formestane. Each of the points represents the mean in each patient of the levels before treatment and between days 7 and 28 (part 1) and days 35–56 (part 2).**

as geometric group means in Fig. 2. Unfortunately, the random assignment of patients to the four doses resulted in markedly different mean pretreatment levels of oestradiol in the four groups. This confounds between dosage group comparisons during the first 4 weeks. A comparison might be made of the data after expression of the on-treatment levels as a percentage of pretreatment levels. However, such analysis assumes that the fall in oestradiol levels is proportional and that the proportional fall is independent of pretreatment levels. The data from the group starting on 125 mg daily refute this: this group had the lowest pretreatment oestradiol levels and the percentage fall in oestradiol during part 2 when all patients were on 250 mg once daily is only about half that in the other three groups. Therefore

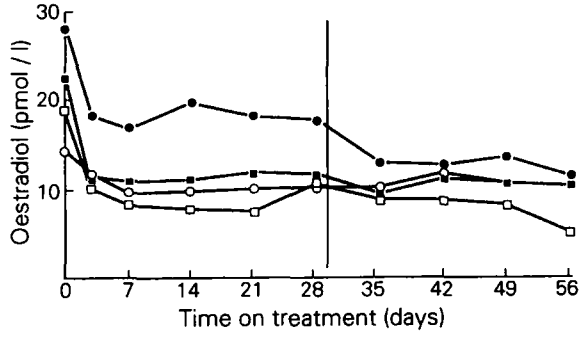


**Fig. 2. Geometric group mean serum levels of oestradiol before and during treatment of postmenopausal breast cancer patients with oral formestane. Error bars are not shown for the sake of clarity. —●— = group A, —○— = group B, —■— = group C, —□— = group D. From day 28, all groups were treated with 250 mg daily.**

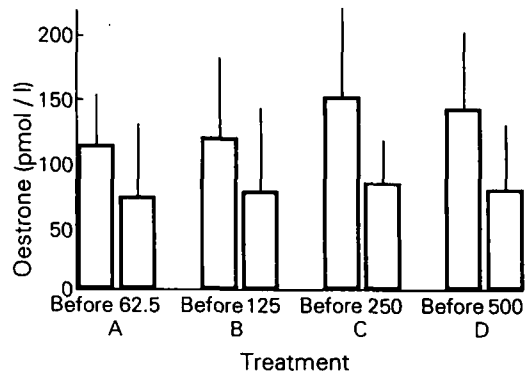


**Fig. 3. Geometric group mean serum levels, (95% confidence intervals) of oestrone before and after 28 days treatment of postmenopausal breast cancer patients with oral formestane.**

the statistical analyses have been confined to within-patient comparisons between the two parts of the study.

All four doses produced a significant fall in oestradiol levels by day 3 ($P<0.001$ for each). From day 7 onwards, there was no further fall during part 1 (Fig. 2). Therefore to obtain a more stable parameter the mean values for each patient between days 7 and 28 were compared with the mean value between day 35 and 56. There appeared to be a fall in oestradiol levels between parts 1 and 2 for the group starting on 62.5 mg formestane daily although this did not reach statistical significance ($P = 0.07$). It is notable, however, that the 5 patients with oestradiol levels above 20 pmol/l during treatment with 62.5 mg, all had lower levels during treatment with 250 mg. For these 5 patients, the oestradiol level during the higher dose treatment was a mean (S.E.) 59(8)% of that during treatment with 62.5 mg. There was no significant change between the two parts for any of the other three groups.

The serum levels of oestrone were significantly suppressed by day 28 ($P<0.001$ for the 62.5 mg, 250 mg and 500 mg doses, respectively and $P<0.01$ for the 125 mg dose, Fig. 3). There was no significant difference between the doses in their on-treatment levels of oestrone.

There were no significant effects on serum levels of aldosterone, cortistol or 17-OHP during the first 28 days of treatment (Table 2). During the second 28 days the mean level of aldosterone in group A was significantly higher than before treatment and in group D the mean level of cortisol was lower than prior to treatment. However, when the data from all patients during part 2 of the study was compared with pretreatment values no significant changes were detected.

The mean level of DHAS was higher during part 1 than before treatment for each of the dosage groups, but this was statistically significant only for groups C and D.

The serum levels of SHBG were not significantly changed for any of the individual groups during treatment except for group D during part 1 (500 mg) when there was a fall from a mean 57.8 nmol/l to 41.8 nmol/l which recovered to 49.2 nmol/l during treatment with 250 mg daily (Table 3). Comparison of the SHBG levels from all patients during their treatment with 250 mg (part 2) showed a significant fall of about 15% from pretreatment levels.

None of the dosage groups showed a significant change from pretreatment levels for either LH or FSH during part 1 of the study (Table 3). However, there were significant increases in both gonadotrophins for some groups during part 2 in compari-

*Table 2. Geometric group means (95% confidence interval) for aldosterone, cortisol, 17-OHP and DHAS, before and during treatment of postmenopausal breast cancer patients*

| Treatment (mg) | Aldosterone | Cortisol | 17 OHP | DHAS |
|---|---|---|---|---|
| Pre | 391 (240–638) | 324 (235–446) | 0.93 (0.66–1.31) | 1.18 (0.50–2.75) |
| 62.5 | 540 (361–807) | 274 (201–373) | 0.91 (0.73–1.13) | 1.85 (1.23–2.77) |
| 250 | 568* (419–771) | 352 (236–526) | | |
| Pre | 376 (255–554) | 347 (270–447) | 0.77 (0.52–1.13) | 1.36 (0.55–3.33) |
| 125 | 471 (371–596) | 341 (251–464) | 0.91 (0.69–1.20) | 2.17 (1.12–4.20) |
| 250 | 374 (265–527) | 299 (209–431) | | |
| Pre | 542 (401–734) | 328 (257–417) | 0.74 (0.52–1.06) | 1.21 (0.66–2.21) |
| 250(i) | 557 (360–862) | 297 (200–443) | 0.83 (0.61–1.12) | 2.10* (1.30–3.39) |
| 250(ii) | 574 (413–796) | 271 (183–401) | | |
| Pre | 512 (363–722) | 340 (232–498) | 0.88 (0.58–1.32) | 2.42 (1.61–3.63) |
| 500 | 532 (406–699) | 306 (241–389) | 1.07 (0.82–1.40) | 4.06* (3.04–5.41) |
| 250 | 469 (319–690) | 227† (155–331) | | |
| All pre | 449 (375–538) | 334 (292–381) | | |
| All 250 | 498 (427–581) | 290 (243–346) | | |

*$P<0.05$, Mean 95% CI. †$P<0.01$.

*Table 3. Geometric group means (95% confidence interval) for SHBG, LH and FSH, before and during treatment of postmenopausal breast cancer patients*

| Treatment (mg) | SHBG | LH | FSH |
|---|---|---|---|
| Pre | 63.8 (38.6–105.2) | 29.6 (14.8–59.0) | 37.8 (17.6–81.4) |
| 62.5 | 70.2 (46.6–105.7) | 36.6 (20.2–66.2) | 46.2 (25.4–84.2) |
| 250 | 58.1 (41.8–80.8) | 49.7* (37.4–66.0) | 66.5* (56.0–79.0) |
| Pre | 96.0 (77.2–119.3) | 34.7 (23.2–51.9) | 26.5 (11.1–63.6) |
| 125 | 89.4 (73.3–109.0) | 34.1 (22.4–51.8) | 28.0 (11.8–66.5) |
| 250 | 77.7 (60.9–99.1) | 43.3 (31.4–59.7) | 52.0 (40.0–67.7) |
| Pre | 59.8 (43.9–81.5) | 15.7 (8.6–28.6) | 16.6 (7.5–36.7) |
| 250(i) | 54.9 (41.6–72.4) | 17.7 (10.8–28.9) | 21.3 (10.5–43.1) |
| 250(ii) | 53.2 (72.7) | 28.2† (18.5–42.9) | 26.7† (13.3–53.5) |
| Pre | 57.8 (39.8–84.0) | 27.8 (12.8–60.2) | 34.0 (17.5–65.9) |
| 500 | 41.8* (29.6–59.0) | 29.8 (14.6–61.1) | 40.0 (24.7–65.1) |
| 250 | 49.2 (31.8–76.1) | 42.8 (33.3–54.9) | 52.9† (40.0–70.0) |
| All pre | 67.4 (56.5–80.5) | 25.7 (19.2–34.5) | 27.5 (19.3–39.2) |
| All 250 | 57.9* (49.5–67.7) | 39.8‡ (33.8–46.8) | 46.4‡ (37.0–58.0) |

*$P<0.05$, †$P<0.01$, ‡$P<0.001$.

son with pretreatment levels. This was highly significant ($P<0.001$) for LH and FSH when the values were compared for all patients.

*Drug levels*

The geometric mean concentration-time profiles of formestane after single oral dosing are shown for the four doses in Fig. 4 and the relationships between the maximum concentration ($C_{max}$) and area under the curve (AUC) with dose are shown in Figs 5(a) and (b). Mean pharmacokinetic parameters are given in Table 4. $C_{max}$ and AUC appeared to relate approximately

*Table 4. Geometric group means (95% confidence intervals) for $C_{max}$ and AUC of formestane after first oral dose in relation to dose administered*

| Dose (mg) | $C_{max}$ (nmol/l) | AUC (nmol h/l) | ERC |
|---|---|---|---|
| 62.5 | 64 (29–143) | 135 (80–228) | 0.335 (0.182–0.616) |
| 125 | 98 (45–213) | 230 (107–496) | 0.449 (0.224–0.899) |
| 250 | 262 (178–388) | 672 (469–963) | 0.389 (0.252–0.600) |
| 500 | 396 (226–694) | 1407 (886–2443) | 0.311 (0.181–0.567) |

ERC = elimination rate constant ($Ke'$).

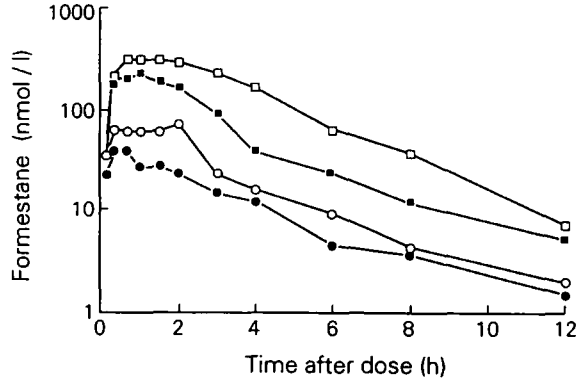


**Fig. 4. Geometric group mean serum levels of formestane during the first 12 hours after the first oral dose of formestane. —●— = group A, —○— = group B, —■— = group C, —□— = group D.**

linearly to administered dose. The AUCs and $C_{max}$ varied widely between patients for each of the doses: for the 125 mg dose the largest AUC was nearly five times that of the smallest. The length of time taken to reach $C_{max}$ increased with the dose administered: median time for 62.5, 125, 250 and 500 mg doses was 0.67, 0.70, 1.00 and 1.50 h, respectively.

The decay phase of the serum formestane concentration/time profile was irregular with more than one peak and trough for most patients. Nevertheless the elimination rate was calculated for each patient following the point of maximal concentration to 12 h postdosing. The mean values are given in Table 4. The elimination rate constant did not vary significantly between doses as can be seen by the parallel nature of the concentration-time profiles during the "terminal phase" (after 4–6 h) (Fig. 4). The mean elimination half-life derived from the overall mean elimination rate constant was approximately 2 h.

Urinary formestane glucuronide levels were measured in urine collections which were pooled during the time intervals 0–4,

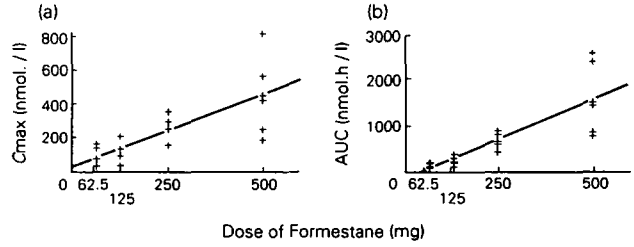


**Fig. 5. Relationship between dose of oral formestane and (a) maximum concentration ($C_{max}$) and (b) area under the curve (AUC) after the first administration of formestane. The line shows the best/least squares fit on linear regression.**

4–8, 8–12 and 12–24 h after administration of the first dose. The mean percentage of formestane recovered in the urine as formestane glucuronide over the cumulative 24 h period was 19.8, 14.0 and 21.4 for the 62.5, 250 and 500 mg doses, respectively. Insufficient samples were available from the patients treated with 125 mg for meaningful analysis. Overall, between 40% and 60% of the cumulative 24 h excretion occurred during the first 4 h.

## DISCUSSION

Previous studies of formestane have indicated that it is an effective suppressant of serum oestradiol levels and a clinically effective treatment for postmenopausal breast cancer [7–11] when given by either the intramuscular or oral route. Larger doses need to be given by the oral route, presumably because of the rapid metabolism of the drug when given by this route [10, 11]. This rapid clearance of the drug was confirmed by the present study. The $C_{max}$, AUC and apparent half-life of formestane with the 250 mg oral dose were similar to those published for our previous study with that dose [11]. In this study an approximately linear change in pharmacokinetic parameters (AUC and $C_{max}$) with dose has also been demonstrated. It can also be seen, however, that both the AUC and $C_{max}$ vary markedly between patients on the same dose, which is likely to lead to a major overlap between the effectiveness of different doses through a patient population. Such between-patient variability reduces the confidence in the interpretation of between-dose comparisons in different patients. Within patient dose comparisons avoid this problem but have the additional problem of possible carryover effects which may be particularly marked if induction of drug metabolism occurs.

Approximately 20% of the dose of formestane appears in the urine as formestane glucuronide within 24 hs after a single oral dose, with very little of this excretion occurring during the second 12 hours. Whilst some of the dose may remain unabsorbed it seems likely that the rest of the absorbed dose is excreted as glucuronides and/or sulphates of steroidal metabolites of formestane, some of which have been identified [16].

The $C_{max}$ and AUC for the 500 mg oral dose of formestane were approximately 4-fold higher in the postmenopausal breast cancer patient than in a group of 6 normal male volunteers (aged 21–22 years) [17]. This is despite the urinary excretion of formestane and the elimination half-life of formestane being similar between the two groups. This indicates that the volume of distribution is greater in the male volunteers than the female patients. Clearly there are age and disease differences between these two groups which may be related to this difference in volume of distribution but it is interesting to note that a similar difference in serum formestane levels was also noted between male and female rats [18].

The main aim of this work was to compare the effectiveness of the four doses of formestane on suppression of serum oestradiol levels. The comparison between dosage groups was complicated by the different pretreatment levels. The comparison of doses was therefore confined to cross-over analysis and comparison against the dose of 250 mg daily. It appears that the low dose of 62.5 mg may not be as effective as the dose of 250 mg. Although the $P$ value of 0.07 does not meet the conventional levels of statistical significance, it was interesting to see that those patients with the highest oestradiol levels on the lower dose all showed a fall in these levels on crossover to 250 mg daily. This is similar to the finding in patients treated with formestane intramuscularly, where those patients with the highest pretreatment levels tended to show the most marked recovery of oestradiol levels 2 weeks after injection [11]. It therefore seems likely that 62.5 mg daily is not as effective as 250 mg for at least some patients.

The pretreatment oestradiol levels for the 125 mg group were very low. Caution should therefore be exercised in interpreting the similarity between the oestradiol levels for these patients between parts 1 and 2 of the study. We are currently performing *in vivo* studies of peripheral aromatisation using radioactive tracer techniques to assess the effectiveness of the 125 and 250 mg doses. The lack of any evidence of better suppression of oestradiol levels by 500 mg daily than by 250 mg confirms our previous observation of no significant difference between 250 mg given once or twice daily [11]. The low pretreatment oestradiol levels in the 125 mg group do not seem to have been due to differences in the age, weight or height of the patients (Table 1).

The measurement of oestrone levels was made by GCMS analysis since earlier analyses by radioimmunoassay in intramuscularly treated patients had spuriously high results [11, 19]. The current results confirm that formestane given by the oral route suppresses both serum oestrone and oestradiol levels as would be expected of an inhibitor of aromatase.

The effect of oral formestane on serum levels of aldosterone, cortisol and 17-OHP has not previously been reported. The only statistically significant changes noted were an increased mean aldosterone level during part 2 of the study in group A and a reduced mean cortisol level in part 2 for group D. These changes were, however, not noted with any of the other doses in either part which suggests that these were chance findings. The lack of an effect of formestane on these parameters indicates that in this respect formestane has advantages over aminoglutethimide which suppresses aldosterone levels and causes marked increases in 17-OHP [3, 4], and CGS 16949A which also causes a degree of aldosterone suppression at doses required for maximum suppression of oestradiol [12].

Statistically significant increases in DHAS levels were measured at each of the highest two doses. Measurements made in patients treated with weekly intramuscular injections of 500 or 1000 mg formestane during early clinical studies with the drug showed a mean increase in DHAS levels of about 25% which was not statistically significant [18]. The changes in that and the current study are difficult to explain in the absence of any other effect on adrenal steroidogenesis. It remains a possibility that these increases might result from crossreaction. Formestane itself does not crossreact at a significant level in the DHAS assay but the measurements were made in untreated serum and unknown water-soluble conjugated metabolites of formestane might contribute to the results.

During part 1 of the study only the 500 mg dose caused a significant reduction in SHBG levels. For each of the sets of observations made in patients on 250 mg daily the mean level of SHBG was reduced. Whilst individually these were not statistically significant when all of the part 2 data were combined a significant fall of about 15% was detected. A decrease in SHBG has previously been found in orally but not parenterally treated patients [11, 19]. This is probably due to the minor androgenic activity of formestane [20] which is likely to have a more marked effect when the drug enters the circulation via the liver, the organ of SHBG synthesis. This 15% decrease in SHBG levels (with what is likely to be the highest oral dose of formestane to be required for therapeutic effectiveness) is likely to lead to only a very small change in the protein binding and biological activity of plasma oestradiol and testosterone.

The increases in gonadotropin levels found in the present study were not noted with either parenterally or orally administered formestane in earlier trials [11, 19]. This is despite the fact that in one previous study [11] higher oral doses than those in the current study were investigated. However, it is notable that the increases in gonadotropin levels in the current study occurred only during part 2, i.e. between 4 and 8 weeks after starting treatment. In the previous study the measurements were made after only 2 weeks. It is probable that the increase in gonadotropins is due to the reduced levels of oestradiol. The delay in occurrence of the increase might be due to the pituitary becoming desensitised to such changes during the menopause and its taking longer to respond to suppressed oestrogen levels. In this regard it is notable that the high gonadotropin levels of the early menopause fall as the menopause advances.

Thus oral administration of formestane is an attractive choice for aromatase inhibition. The appropriate dose for oestrogen suppression is probably either 125 or 250 mg daily and at this dose there are few if any significant endocrine side-effects. Previous studies have demonstrated the clinical effectiveness and low toxicity of the 500 mg daily dose [8] and this has now been confirmed for the 250 mg dose (data not shown). Further studies are required to select the optimum dose and these are probably best conducted by radioactive tracer studies of peripheral aromatisation. Additional investigations are also required to characterise the metabolic fate of formestane and to explain the sex-related differences in pharmacokinetics.


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