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# The Influence of Intramuscular 4-Hydroxyandrostenedione on Peripheral Aromatisation in Breast Cancer Patients

**A.L. Jones, F. MacNeill, S. Jacobs, P.E. Lonning, M. Dowsett and T.J. Powles**

**The influence of the aromatase inhibitor 4-hydroxyandrostenedione (4OHA) given intramuscularly on the peripheral aromatisation of androstenedione into oestrone was investigated in postmenopausal women with breast cancer and compared with the suppression of plasma oestradiol ($E_2$). 7 patients were investigated before and during treatment on day 7, i.e. midway between two weekly injections. After an intravenous injection of [$^3$H] androstenedione and [$^{14}$C] oestrone, urine was collected for 96 h and the isotope ratio determined in the urinary oestrogen metabolites after isolation with high performance liquid chromatography. At 250 mg, 4OHA inhibited aromatisation to [mean (S.D.)] 15.2 (5)% of baseline ($P < 0.002$). There was significantly greater inhibition to 8.1 (2.7)% at 4OHA 500 mg ($P < 0.01$). Plasma $E_2$ was reduced to 41.2 (14.1)% of baseline at 4OHA 250 mg with a further reduction to 32.7 (19.8)% at 500 mg ($P < 0.05$). These results confirm the dose–response relation previously established with plasma oestrogen measurements alone.**
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## INTRODUCTION

ENDOCRINE TREATMENT is frequently used as first line therapy in postmenopausal women with advanced breast cancer. Most forms of endocrine therapy work by reducing the oestrogenic stimulation of breast cancer cells, either by antagonism of oestrogen receptors within the cells or by the reduction of the circulating oestrogen available to the cancer cell [1]. In postmenopausal women, the major pathway of oestrogen production is through the peripheral conversion of androstenedione produced in the adrenal gland and ovary to oestrogens [2]. This process of aromatisation occurs in several tissues through the actions of the aromatase enzyme complex. A number of selective inhibitors of aromatase have been developed and are under laboratory and clinical evaluation.

Aminoglutethemide, now regarded as a prototype aromatase inhibitor, has been shown to inhibit peripheral aromatisation *in vivo* by approximately 95% [3] with a reduction in plasma oestrogen levels to approximately 30% of pretreatment values [4]. The response rate in patients with advanced breast cancer treated with aminoglutethemide is around 30% and is similar to the response rate which is achieved with tamoxifen [5–7]. The side-effects of aminoglutethemide, including rash, ataxia and bone marrow suppression, may be clinically important. Aminoglutethimide may also influence the disposition of other drugs [5]. The inhibition of other steroid hydroxylases by aminoglutethemide, due to its interaction with other cytochrome P450s [8], means that aminoglutethemide has to be given in combination with glucocorticosteroid for safety and maximal suppression of plasma oestrogen levels [9]. New drugs are under development in order to identify an effective and more specific aromatase inhibitor with a lower toxicity profile.

4-Hydroxyandrostenedione (4OHA, CGP 32349, Ciba Geigy) is a suicide inhibitor of aromatase and is more potent than aminoglutethimide *in vitro* [10]. 4OHA has been shown to be of clinical use in breast cancer patients when given by either the oral or intramuscular route [10–13]. In a study comparing 250 mg with 500 mg 4OHA intramuscularly given every 14 days, the maximal suppression of plasma oestradiol levels was

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similar for the two doses but significant recovery occurred just prior to the second and third injection with the 250 mg, but not with the 500 mg dose [11]. In a non-randomised clinical study there was no difference in the response rate (33%) between these two dose levels, however, the incidence of side-effects with pain and formation of lumps at the injection was less at the 250 mg dosage every 14 days [12] and this has been adopted as the dose and schedule for parenteral use.

The use of plasma oestrogen levels to compare the efficacy of different doses of an aromatase inhibitor or to compare different drugs is a relatively crude method of assessment partly because of inter patient variation in pretreatment levels and partly due to the technical difficulty of measuring very low post menopausal oestrogen levels. Also, it should be considered that plasma oestrogens only indirectly reflect the hormone production rate, as these may also vary with alterations in oestrogen metabolism [14]. Accordingly, there is a need to assess aromatisation directly by use of tracer methods. The use of *in vivo* tracer studies which measure urinary oestrogen conjugates over a prolonged time period has been reported to be a reliable method of assessing peripheral aromatisation *in vivo* with intra and interpatient assay coefficients of variation of less than 5% [15]. This urinary isotope tracer method has been used in this study to compare the inhibition of peripheral aromatisation caused by two different doses of 4OHA (250 and 500 mg) given parenterally.

## PATIENTS AND METHODS

*Patients*

7 postmenopausal patients with advanced breast cancer who were considered suitable for endocrine treatment were enrolled in the study. The protocol was approved by the Royal Marsden Hospital ethical committee and all patients gave informed consent. The median age was 69 (range 56–84) years and mean body weight at the start of treatment was 54 (range 50–71) kg. All patients had undergone a spontaneous menopause at least 2 years prior to the study. All patients had received prior endocrine therapy with tamoxifen (20 mg orally per day) and most had received prior chemotherapy, however no systemic anticancer treatment or radiotherapy had been given within 4 weeks of commencing this study.

*Drug*

Patients were treated with 4OHA intramuscularly every 14 days. 4OHA was provided by Ciba-Geigy Pharmaceuticals as a sterile microcrystalline formulation and suspended in 0.9% saline immediately prior to intramuscular injection (125 mg/ml). 4 patients were started on 250 mg and after three injections (6 weeks of treatment), the dose was increased to 500 mg. 3 patients were started on 500 mg and the dose reduced to 250 mg after three injections. *In vivo* aromatisation was measured before treatment and on day 7 after the third injection (i.e. midway between doses) at each dose level in all patients. Patients were then maintained on their final dose, provided there was no evidence of disease progression.

*Chemicals*

Solvents were obtained from BDH Dagenham and were of analytical or HPLC grade. [6,7-$^3$H] androstenedione (A) (1.52 MBq/mmole) was a gift from Ciba-Geigy Pharmaceuticals, Horsham, Sussex (courtesy of Dr R. Wade). [4-$^{14}$C] oestrone ($E_1$) (50–60 1.85–2.22 GBq/mmole) was obtained from New England Nuclear. DEAE-Sephadex was obtained from Pharmacia Ltd.

*Investigation protocol*

Patients were given an intravenous bolus of 18.5 KBq [4-$^{14}$C] $E_1$ and 18.5 GBq [6,7-$^3$H] A dissolved in 50 ml saline/ethanol (92:8 w/w) over 10–15 min using a glass syringe and a teflon cannula. The vehicle was prepared as follows: ethanol and [$^{14}$C] oestrone were added to 50 ml of saline. To avoid [$^3$H] cross over in the $^{14}$C channel, four 50 μl aliquots of the injection mixture were retained prior to addition of [6,7-$^3$H] A for scintillation counting and another four aliquots were obtained after the [6,7-$^3$H]A was added for estimation of [$^3$H] in the injection mixture. After injection, patients collected all their urine in plastic containers for 96 h. The total volume of the pooled urine for each patient was measured and two 800 ml aliquots were frozen at −20°C until analysis. Plasma samples were taken from the contralateral arm immediately prior to the injection of radioisotope tracer pretreatment and at each study on treatment for estimation of plasma oestradiol ($E_2$). Plasma samples were taken before treatment and on day 7 after the third injection at each dose level.

*Urine analysis*

A detailed description of the analytical method and its reproducibility has been described previously [15]. In brief, the pooled urine samples were thawed and urinary steroid glucuronides were concentrated using Sep-pak C-18 cartridges and a preparative DEAE Sephadex A-25 column eluted by a salt gradient. The glucuronides were hydrolysed with 1 ml (144 000 units) β-glucuronidase (Sigma, C-8885) at 37°C for 48 h and the unconjugated oestrogens were separated from androgens on two further DEAE Sephadex A-25 columns using acetate buffer/methanol mixtures as eluent. Oestrone ($E_1$), oestradiol ($E_2$) and oestriol ($E_3$) were separated by reverse phase high performance liquid chromatography (HPLC) using a Hypersil ODS 5 μm (Chrompack) 4.6 × 250 mm column and a mobile phase of acetonitrile/phosphate buffer 0.05M pH 3 [16].

*Liquid scintillation counting*

Samples were counted in a Tricarb 1900 CA liquid scintillation counter using automatic quench calibration. Each sample was counted in a 10 ml plastic vial with emulsifier-safe scintillation fluid (Packard). There was a crossover of 0.2–0.4% of $^3$H in the $^{14}$C channel, but no crossover of $^{14}$C in the $^3$H channel.

*Pharmacokinetics calculations*

The $^3$H/$^{14}$C ratio was calculated for each individual oestrogen ($E_1$, $E_2$ and $E_3$) and compared with the injection mixture to derive the percentage aromatisation according to the formula

$$\% \text{ aromatisation} = \frac{([^3H]/[^{14}C]) \text{ urine metabolite} \times 100}{([^3H]/[^{14}C]) \text{ injection mixture}}.$$

The final figure for percentage aromatisation was taken as the mean of the figures for $E_1 + E_3$, since the 3H–$E_2$ in on-treatment samples was frequently too low to quantify aromatisation for $E_2$ with confidence.

*Oestradiol assay.* This was performed according to a method previously described [11].

*Statistical methods*

The Friedman analysis of variance was used to test the hypothesis of no difference between the treatments. If this revealed a significant difference between the three treatments,

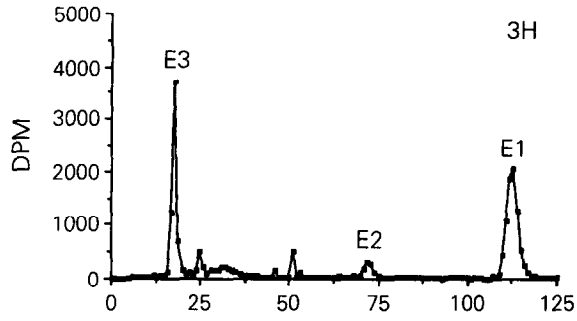


**Fig. 1. Aromatisation of androstenedione to oestrogen metabolites pretreatment.**

paired comparisons were done by the Wilcoxon matched-pairs signed-ranks test using a Bonferroni correction for the final $P$ value. $P$ values for the overall comparison were expressed as two-tailed but $P$ values for paired comparison were expressed as one-tailed, as the test hypotheses for paired comparisons were considered to be whether $X_n \geq X_{n+1}$ and not $X_n = X_{n+1}$.

## RESULTS

A typical radiochromatogram of the urine from a patient in the control situation is shown in Fig. 1a and b. There is close agreement with the results obtained for the separate tritium and $^{14}$C-labelled oestrogen metabolites and values could be determined for oestrone ($E_1$), oestradiol ($E_2$) and oestriol ($E_3$). When patients were receiving treatment with 4OHA, the isotope ratio could be determined for both the $E_1$ and $E_3$ fractions, however the isotope ratio for the $E_2$ fraction was much lower on treatment and therefore values for $E_2$ frequently could not be quantified individually with confidence.

The levels of percentage aromatisation before treatment with 4OHA and at each dose level are expressed as the mean of $E_1$ and $E_3$ in Table 1. All patients showed a significant reduction in aromatisation on treatment ($P < 0.005$) and 6 out of 7 patients showed a greater reduction on the 500 mg dose compared with 250 mg ($P < 0.05$). This represents a reduction in aromatisation to [mean (S.D.)] 15.2 (5.0)% of baseline at 4OHA 250 mg ($P < 0.025$) and to 8.1(2.7)% of baseline at 4OHA 500 mg ($P < 0.025$). This reduction is represented in Fig. 2(a).

The plasma levels of $E_2$ pretreatment and on each dose are shown in Table 2. There was a wide interpatient variation from 8.4 to 33.7 pmol/l for the pretreatment value. Despite the

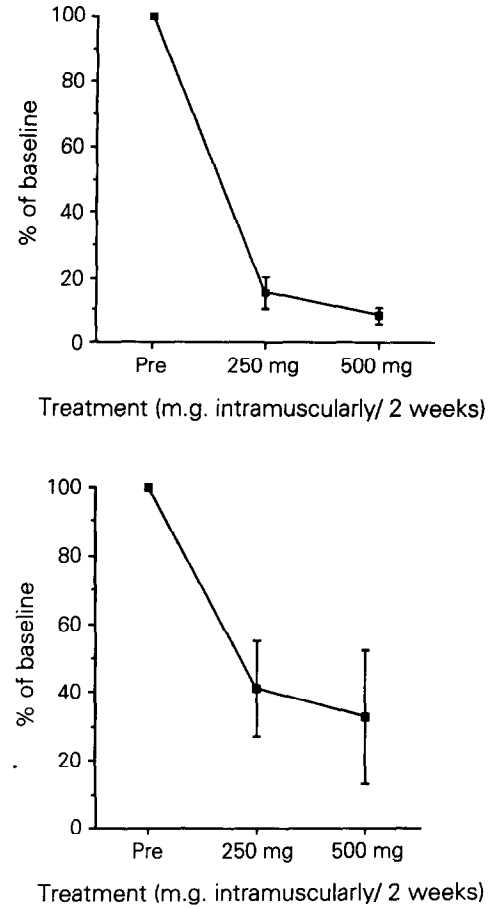


**Fig. 2. (a) Inhibition of aromatisation by 4OHA expressed as a percentage of baseline for urinary isotope ($E_1$ + $E_3$). (b) Reduction of plasma $E_2$ on 4OHA expressed as a percentage of baseline values.**

greater than 80% inhibition of peripheral aromatase activity demonstrated by the urinary isotope studies, plasma $E_2$ was still detectable on treatment at both doses of 4OHA, although there was a significant reduction for on-treatment $E_2$ levels compared with pretreatment levels ($P < 0.025$). There was a reduction in plasma $E_2$ to a mean of 41.2 (14.1)% of baseline on 4OHA 250 mg ($0.05 < P < 0.10$) and to 32 (19.8)% on 4OHA 500 mg (Fig. 2b).

A comparison of the changes in percentage aromatisation for individual patients on treatment for both urinary aromatisation

*Table 1. Percentage aromatisation measured from urinary isotope ratios of the mean ($E_1$ and $E_3$) on treatment with 4-hydroxyandrostenedione (4OHA)*

| Patient | Pretreatment | 4OHA 250 mg | 4OHA 500 mg |
|---|---|---|---|
| 1 | 4.25 | 0.37 | 0.21 |
| 2 | 2.68 | 0.33 | 0.15 |
| 3 | 4.03 | 0.73 | 0.49 |
| 4 | 2.38 | 0.47 | 0.14 |
| 5 | 1.82 | 0.19 | 0.19 |
| 6 | 1.17 | 0.26 | 0.10 |
| 7 | 1.65 | 0.24 | 0.15 |
| Mean (S.D.) | 2.57(1.18) | 0.37(0.18) | 0.20(1.13) |

Patients 1–4 started at 250 mg and increased to 500 mg. Patients 5–7 started at 500 mg and decreased to 250 mg.

*Table 2. Changes in plasma oestradiol ($E_2$ pmol/l) on 4-hydroxyandrostenedione (4 OHA)*

| Patient | Pretreatment | 4OHA 250 mg | 4OHA 500 mg |
|---|---|---|---|
| 1 | 24.80 | 9.30 | 8.10 |
| 2 | 20.50 | 6.90 | 4.60 |
| 3 | 33.70 | 8.00 | 5.40 |
| 4 | 17.80 | NA† | 4.30 |
| 5 | 8.40 | 4.80 | 6.00 |
| 6 | 9.40 | 10.85 | 7.30 |
| 7 | 11.10 | 6.00 | 3.30 |
| Mean (S.D.) | 17.96(9.24) | 7.64(2.21) | 5.57(1.70) |

Patients 1–4 started at 250 mg and increased to 500 mg. Patients 5–7 started at 500 mg and decreased to 250 mg.
† Sample not available.

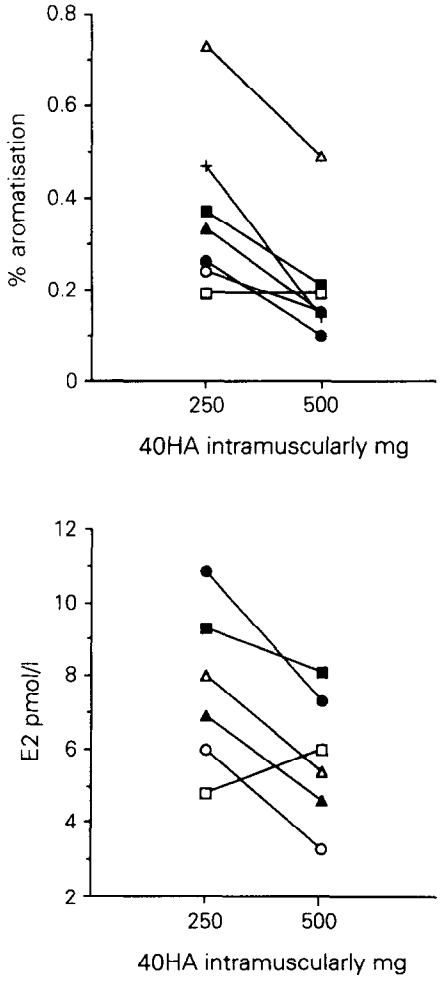


**Fig. 3. (a) Inhibition of aromatisation for individuals on treatment. The symbols represent the same patient as in panel (b). (b) Inhibition of plasma $E_2$ for individuals on treatment. The symbols represent the same patients in panel (a).**

($E_1$ and $E_3$) and plasma $E_2$ is shown in Fig. 3a and b, respectively. This shows that the urinary results confirm the results for plasma $E_2$ suppression for individual patients. Patient 5 who did not show any further suppression in plasma $E_2$ with the dose escalation also had no further suppression of urinary aromatisation. The dose administered in the two treatment situations has been confirmed for this patient.

## DISCUSSION

4-Hydroxyandrostenedione has clinical efficacy in the treatment of advanced breast cancer and parenteral treatment with 4OHA does not affect other steroid hydroxylase systems [10, 17]. Previous comparisons of 4OHA 250 mg with 500 mg administered intramuscularly every 14 days have indicated that the 250 mg dose might not maintain maximal suppression of plasma oestradiol throughout the 14-day period between injections. However, the marginal nature of this and clinical considerations of response and local side-effects have resulted in the lower dose being used in phase III studies.

The urinary method used to assess peripheral aromatisation in this study allows assessment of aromatisation over 96 h, thus avoiding any short-term influences and also allows determination of the isotope ratio in different urine metabolites. This method has been shown to be reliable and reproducible [15]. In a previous dose comparison study of another aromatase inhibitor (CGS16949A) this urinary tracer method [15] confirmed the dose-related suppression of aromatase which had previously been indicated (indirectly) with studies of plasma oestradiol [18].

In the current study the infusions covered the period days 7–11 after injection of 4OHA, therefore, it would be expected that any recovery occurring during the second week would be detected. Our results show that the inhibition of aromatisation was significantly greater at 4OHA 500 mg than 250 mg. The results at the higher dose are comparable with those previously reported for 4OHA using radioactive tracer infusion studies [19] and are also in the range of the >90% aromatase inhibition reported with aminoglutethemide [3, 20]. The decrease in plasma oestradiol by nearly 70% of baseline values in this study is in agreement with previous reports [10, 17, 19] of changes in oestradiol with 4OHA. Plasma samples were taken 7 days after injection, i.e. at the time of maximal suppression [10]. 1 patient failed to show any suppression at 250 mg. Although there was a greater reduction in plasma oestradiol at the higher dose, the difference was not significant, however this may be a result of low patient numbers in this study.

In conclusion, our results confirm that 4OHA causes a dose-dependent aromatase inhibition in the 250–500 mg dose range given every 14 days and that this decrease parallels plasma $E_2$ suppression. The degree of inhibition of aromatisation required for maximal clinical efficacy is uncertain but theoretically greater inhibition would be expected to be more effective. If the 500 mg dose had been as acceptable as the 250 mg dose in the clinic, this would have been the dose of choice on the basis of endocrine and metabolic data. This radioisotope tracer method allows dose and drug comparison studies of endocrine efficacy using a small number of patients and is a useful adjunct in dose selection for aromatase inhibitors.

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# Thyroid Function 10–18 Years after Mantle Field Irradiation for Hodgkin's Disease

**Pauline F. Peerboom, Elly A.M. Hassink, Rein Melkert, Luc DeWit, Wim J. Nooijen and Peter F. Bruning**

**Thyroid function was measured in 81 patients who had been curatively irradiated on a mantle field for Hodgkin's disease 10–18 years ago. 47 patients (58%) had elevated levels of thyroid stimulating hormone, indicating hypofunction of the thyroid gland, compared with 4.6% of controls (hospital visitors) matched for age and sex. The mean free thyroxine index (FTI) was significantly lower in patients than in controls, but all FTI values were still normal. Age at the time of irradiation, sex, time since irradiation and administration of chemotherapy were not significant factors in the development of thyroid dysfunction. A life-long awareness of the possibility of insidiously developing myxedema in these patients is strongly advocated.**
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## INTRODUCTION

FOR A long time, radiation therapy has been an important treatment modality for Hodgkin's disease. One of the possible late side-effects is thyroid dysfunction. The most frequently reported late complication is hypothyroidism [1–10]. Less often, benign thyroid nodularity and thyroid carcinoma have been described [2–4, 6, 7, 11, 12].

We report on thyroid function as part of an elaborate evaluation of late sequelae from curative radiotherapy for Hodgkin's disease 10–18 years ago. Also, the influence of age at the time of treatment, sex, chemotherapy and time since irradiation were studied.

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## PATIENTS AND METHODS

Between January 1990 and October 1990, thyroid function was evaluated in 190 individuals. Of these 190 individuals, 81 had received mantle field irradiation for Hodgkin's disease 10 to 18 years previously, in the Netherlands Cancer Institute. During the diagnostic work-up, all patients underwent lymphangiography. All were still free of disease at the time of the study. The limit of 18 years was chosen since, from 1972 onwards, all patients were irradiated with a linear accelerator.

The study group consisted of 42 males, aged 25–69 years, [mean (SD) 43.5 (10.0)], and 39 females, aged 29 to 72 years [mean (SD) 42.8 (11.0)]. Mean follow-up time was 14 (2.5) years. All patients had received mantle field irradiation, which included the entire thyroid gland. They received 20–40 Gy (86.2% received 40 Gy), over a 3–6 week period. 19 patients were also treated with chemotherapy after irradiation. Vinblastin was given weekly for 2 years to 5 patients; mustine, vincristine, prednisone, procarbazine (MOPP) was given to 14 patients every 4 weeks for four to six cycles.

As controls, 116 hospital visitors were carefully matched for