between smoking and dying is the long delay between cause and effect. Around the world, women generally start smoking later than men. So, whereas the increases in the numbers of men dying because of tobacco are largely due to population growth, the numbers of women dying is because of an increasing death rate due to smoking. Although the EC 'leads' for the highest number of men dying due to tobacco (466 000 predicted for 1995), the USA has the largest number of female deaths, with forecasts of 318 000 men and 240 000 women dying in 1995 because of smoking.

Peto and colleagues also forecast to the year 2025. For all developed countries at current smoking patterns, the tobacco-related deaths in 2025 could be 2.6 million for men and 0.8 million for women. However, if the female death rate rises at present trends, the figure for females could be over 1 million. For less developed countries, the investigators estimate the numbers at 5–10 million.

The tragedy for smokers is not only that they misunderstand (or perhaps have been misled) about the risks, but they also do not realise the benefits of stopping. "Those who stop before they have cancer or serious heart or lung disease avoid most of their risk of death from tobacco," stated Peto.

Premature death due to tobacco is an avoidable disaster. We must act aggressively now against tobacco use. Otherwise, as Dr Antonio Novello, US surgeon General, says, "We will fail the generations of tomorrow." In November, the EC has the opportunity to take another sort of lead, when member states meet to vote to ban tobacco advertising.

David McNamee
Former Scientific Editor
European Journal of Cancer

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Papers

4-Hydroxyandrostenedione: A New Treatment for Postmenopausal Patients with Breast Cancer

R. Charles Coombes, Stuart W.M. Hughes and M. Dowsett

We have evaluated 4-hydroxyandrostenedione, a specific inhibitor of aromatase, as treatment for breast cancer in a phase I dose-ranging study and a phase II study of the best-tolerated dose. 168 postmenopausal patients with locally advanced and metastatic breast cancer were treated intramuscularly. 19% of patients attained a complete or partial response but 26% of those who completed at least 4 weeks treatment responded. Side-effects were least in the group receiving 250 mg every 2 weeks. 13% of patients experienced local discomfort due to the injection and 5% had other side-effects. Serum oestradiol fell to 42.4 and 26.5% of baseline at 7 days after the start of treatment with the 250 mg and 500 mg dose, respectively. We conclude that 4-hydroxyandrostenedione at 250 mg every 2 weeks is a safe and effective form of treatment for postmenopausal patients with metastatic breast cancer.
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INTRODUCTION

IT IS GENERALLY ACCEPTED that tamoxifen is the first-line treatment for postmenopausal patients with advanced breast cancer. However, there is need for an effective second-line endocrine therapy for two reasons. Firstly, all patients eventually become resistant to tamoxifen and often relapse with metastatic breast cancer that is still hormone sensitive, and secondly more patients now have their first relapse with tamoxifen-resistant metastatic disease since often they have received tamoxifen immediately postoperatively and have relapsed despite this therapy.

Conventional treatment for these patients includes progesterone preparations (e.g. medroxyprogesterone acetate) or steroid synthesis inhibitors such as aminoglutethimide. However, these therapies often cause side-effects. The most troublesome are fluid retention and psychological side-effects for progesterone preparations [1] and inhibition of cortisol synthesis, drowsiness and skin rashes for aminoglutethimide [2].

Our strategy has been to develop a 'pure' inhibitor of the aromatase enzyme system which possesses neither the sedative effects nor the other non-specific enzyme inhibitory effects of aminoglutethimide.

Oestrogens in postmenopausal women are derived mainly

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from the conversion of adrenal-derived androgens, primarily androstenedione and testosterone, to oestrone (E1) and oestradiol (E2), respectively (Fig. 1). This conversion is catalysed by the aromatase enzyme and in this group takes place in peripheral tissues including adipose tissue, muscle, and normal breast tissue and breast cancer tissue itself (Silva *et al.*). 4-Hydroxyandrostenedione (4OHA) has been shown by to be a specific protein inhibitor of the enzyme and to possess only minor steroidal effects by virtue of its weak binding to the androgen receptor (*ca.* 1% compared to 5α-dihydrotestosterone). Furthermore the compound has been shown to cause regression of endocrine-sensitive rat mammary tumours [3, 4].

We carried out the first studies in patients with breast cancer in 1984 and showed that 4OHA was effective in reducing oestradiol levels and in causing marked regression of human breast cancer [5]. Further studies confirmed that most patients, after a single injection, maintained full oestradiol suppression for at least 2 weeks but all but 1 patient showed at least partial recovery by day 28. It was demonstrated that serum levels of 4OHA were below 3 ng/ml in all patients when recovery began [6]. A dose of 125 mg 4OHA was less effective. Thus further studies, as discussed here, were confined to the doses of 250 and 500 mg.

The aims of this study were to determine (a) the correct dose and schedule for parenteral 4OHA, (b) the side-effects of 4OHA at the chosen dose and (c) the effectiveness of the drug in postmenopausal patients with advanced breast cancer. All protocols involving 4OHA had Ethics Committee approval. Informed consent was obtained from all patients in these studies.

PATIENTS AND METHODS

Patients

Details of the patients studied are shown in Table 1. 186 patients received one of three doses: 500 mg intramuscularly every week (61 patients); 500 mg intramuscularly every 2 weeks (29 patients), and 250 mg intramuscularly every 2 weeks (96 patients). The mean age of the women in each group was similar and 48% received some form of endocrine therapy previously for locally advanced or metastatic breast cancer. 34 women had their periods artificially terminated by oophorectomy in the past. The remaining women were naturally postmenopausal.

Assessment of response to treatment

All patients were fully staged before, at 3 months and 6 months thereafter, including at the end of the study. The staging procedure has been previously documented and consists of chest and skeletal radiology, full haematology and biochemistry and CT scan of liver, together with clinical examination and measurement of all measurable lesions. Assessment of response was according to [7]. Thus, a complete or partial response was defined as complete disappearance and, respectively, a 50% reduction in bidimensional diameter of amenable lesions notified on two separate occasions at least 1 month apart. The 'no change' category referred to patients whose disease had stabilised for at least this period of time.

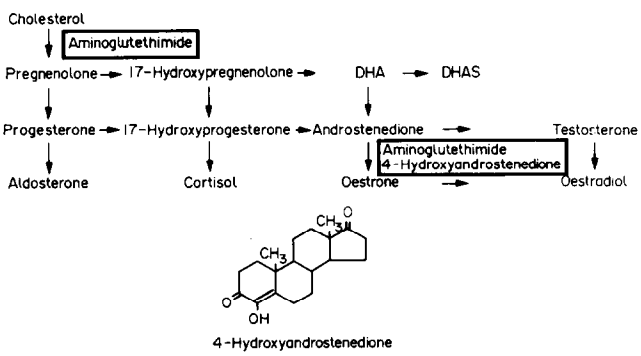

Fig. 1. Sites of steroid synthesis inhibition by aminoglutethimide and 4-hydroxyandrostenedione onward. This figure also shows the structure of 4-hydroxyandrostenedione.

Table 1. Characteristics of patients in parenteral 4-hydroxyandrostenedione trial

	Dose/schedule		
	500 mg weekly	500 mg fortnightly	250 mg fortnightly
No. of patients	61	29	96
Age (mean)	63	66	67
range	37–88	33–88	35–92
Previous adjuvant tamoxifen	3	1	15
Prior endocrine treatment for advanced disease	29 (47.5)	12 (41.4)	49 (51)
More than one endocrine treatment in past	17	6	14
Postmenopausal status			
Natural	43	28	81
Ovariectomy	18	1	15
ER status-positive	25 (41%)	8 (28%)	35 (36%)

Pharmacokinetic studies

For these and all the ensuing studies, 4OHA was supplied by Ciba Geigy Ltd, Basel, Switzerland, in the form of sterile, lyophilised microcrystalline material in vials each containing 250 mg for reconstitution in 2 ml physiological saline for intramuscular injection. Serum levels of 4OHA were measured by radioimmunoassay which has previously been described [6]. Blood samples were taken 1, 2, 4, 7, 10 and 14 days after the first injection of 4OHA from 21 patients treated with a 250 mg dose and 18 treated with 500 mg. Further samples were then taken at intervals of 7 days for a total of 10 weeks. Blood samples taken on the day of injection were taken before the injection was given.

Endocrine studies

Blood samples were drawn from patients before and at intervals during treatment for the measurement of serum levels of oestradiol and oestrone as an indication of the pharmacological effectiveness of treatment. Oestradiol levels were measured by a highly sensitive radioimmunoassay [6] and oestrone by gas chromatography–mass spectrometry [8]. Serum levels of dehydroepiandrosterone sulphate (DHAS), androstenedione, testosterone, 5-alpha-dihydrotestosterone, luteinising hormone (LH) and follicle-stimulating hormone (FSH) and sex-hormone-binding-globulin (SHBG) were measured by previously described radioimmunoassays [1, 8].

Table 2. 4-Hydroxyandrostenedione: results of treatment

	Dose/schedule					
	500 mg weekly		500 mg fortnightly		250 mg fortnightly	
No. of patients	61		29		96	
Responses in all patients (i.e. intention to treat basis)						
CR	2		1		3	
PR	9	18%	6	24.1%	14	17.7%
NC	7		6		15	
PD	40		11		53	
Non-evaluable*	3		5		11	
Totals	61		29		96	
Response in patients receiving treatment for at least 4 weeks						
CR	2		1		3	
PR	9	27.5%	6	29.2%	14	23.6%
NC	7		6		15	
PD	22		11		40	
Totals	40		24		72	

* See text for reasons for non-evaluability.

RESULTS

Results of treatment

Table 2 reviews the results obtained in the three dose schedules used for all evaluable patients and for patients who completed at least 4 weeks treatment. 19 patients (10%) were not considered evaluable for response because of concomitant anticancer therapy (5), poor tolerability after the first injection (5), refusal of a second injection (2), lost to follow-up (3), or concomitant severe disease (4).

The overall response (CR and PR) in evaluable patients was 19% and not significantly different between the three groups. Table 3 shows the minimum, maximum and median duration of response to the three dose schedules. No significant difference was seen.

In the 136 patients who received therapy for at least 4 weeks, the complete and partial response rate was 26% (Table 2). A major determinant of response was the ER status of the primary or recurrent tumour. Thus, 13 (93%) objective responders whose ER status was known had ER-positive tumours, compared with only 37/56 (66%) of patients whose disease worsened on therapy.

In terms of sites of diseases 12/102 (11%) of bone metastases showed healing compared with none of 46 liver metastatic sites.

Table 3. Parenteral 4-hydroxyandrostenedione study. Duration of response (days) for patients who responded (CR, PR) or stabilised (NC) on treatment

Group	Maximum	Median	Minimum
500 mg weekly	596	323	42
500 mg 2-weekly	758	329	58
250 mg 2-weekly	1133	418	97

Table 4. 4-Hydroxyandrostenedione: side-effects of therapy

Dose	500 mg weekly		500 mg 2 weekly		250 mg 2 weekly	
No. of patients	61		29		96	
Side-effect						
Local side-effects						
Pain in buttock	10		2		4	
Sterile abscess	4	31%	1	10%	3	13%
Induration at injection site	5		–		6	
Other side-effects						
Anaphylactoid reaction	3		1		1	
Myositis	0		0		1	
Hirsutes	2	23%	0	10%	0	5%
Lethargy	5		1		2	
Hot flushes	4		1		1	

Local recurrence or contralateral breast carcinomas seemed to respond well with 26% responding.

Another determinant of response was prior response to therapy. Thus, 33 patients had demonstrated a response previously and of these 11 (33%) responded, compared with only 2/35 (6%) patients who clearly failed to respond to prior endocrine treatment.

In general the drug was extremely well tolerated, with only a minority (see Table 4) having any adverse effects. Local side-effects were common with the higher doses but with the lower dose of 250 mg every 2 weeks, only 13% of patients complained of local side-effects, principally pain and/or inflammation at the site of injection. Other side-effects included an analphylactoid reaction in 5 patients, presumably due to inadvertent intravenous administration in some cases which could be avoided by greater care with intramuscular admininstration and a single case of myositis, which resolved on discontinuing therapy. Only one patient demonstrated androgenic side-effects (at the highest dose) and was taking phenytoin at this time.

18 patients (10%) had to discontinue treatment due to side-effects. At the lower dose of 250 mg intramuscularly every 2 weeks, only 4/96 (4%) had to stop treatment.

Endocrine and pharmacokinetic results

Serum levels of oestradiol were suppressed to a mean 37.1 (4.9 SEM)% of baseline 7 days after the first injection in 11 patients treated with 500 mg 4OHA intramuscularly every week. In measurements taken during the subsequent 7 weeks there was no indication of an increase in the degree of suppression nor any evidence of any recovery. The effect of 250 and 500 mg 4OHA every 2 weeks in 40 postmenopausal patients is compared in Fig. 2. By day 7 the mean serum levels of oestradiol were 9.2 (1.5) pmol/l [26.5 (3.0)% of baseline] and 8.7 (0.9) pmol/l [42.4 (7.2)% of baseline] for the higher and lower doses, respectively.

Thereafter, levels were maintained below 50% of baseline throughout the next 9 weeks in both groups. However the suppression was more variable between time points with 250 mg than 500 mg, apparent partial recovery of oestradiol levels occurring prior to injection for the lower but not the higher dose. Mathematical estimates indicated that over the 2-week treatment interval this recovery phenomenon led to a mean

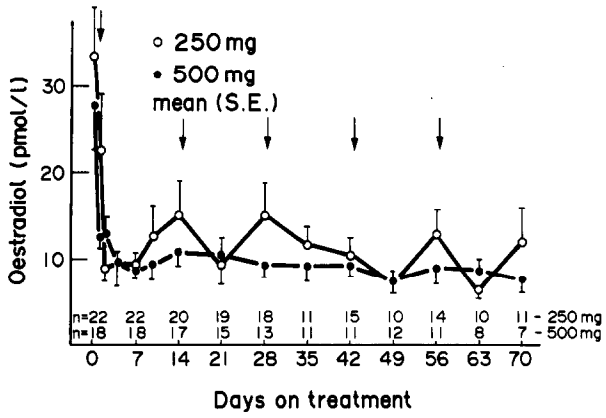

Fig. 2. Serum oestradiol levels (±SEM) following treatment with either 4-OHA 250 mg intramuscularly fortnightly (○) or 500 mg fortnightly (●). Arrows indicate time of injections.

reduction in the degree of suppression of no greater than 8% [8].

Serum 4OHA levels measured in the same group of patients on 250 and 500 mg every 2 weeks showed mean maximal levels during the first and second day after injection with a fall to less than 50% of peak levels by day 4 (Fig. 3). Thereafter the fall in serum 4OHA levels was slower and approximately log-linear with an apparent half-life of between 5 and 10 days. Values for the 250 mg group were parallel to those of the 500 mg group and were approximately half those of the higher dose group. Measurements made during further treatment indicated that there may have been an accumulation of the drug in patients treated with 250 mg but this was not confirmed in patients on 500 mg.

Serum levels of oestrone were measured by GCMS in 9 patients before and during their treatment with 250 or 500 mg every 2 weeks. The level in all patients fell to a mean 40.3 (7.0)% of baseline and was thus closely parallel to the fall in oestradiol levels noted in the same patients.

DHAS, LH, FSH and SHBG levels were measured in the patients on 500 mg every week and no changes were noted. Similarly in patients on 250 and 500 mg every 2 weeks there were no significant changes in the serum levels of androstenedione, testosterone and 5-alpha-DHT.

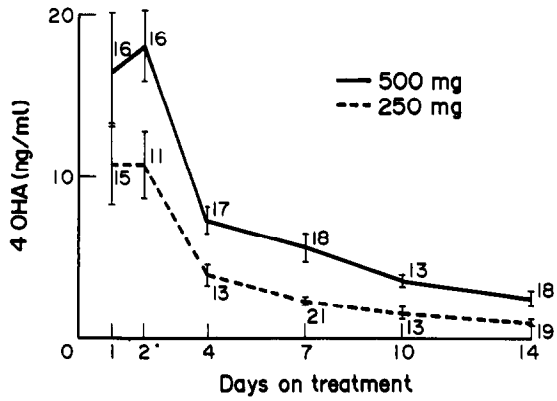

Fig. 3. Serum 4-OHA in postmenopausal patients with breast cancer (±SEM). The solid bar indicates the levels after a single injection of 500 mg and interrupted indicates the levels after a single injection of 250 mg.

DISCUSSION

These studies shows that 4OHA is a safe, well-tolerated and effective endocrine therapy for postmenopausal patients with advanced breast cancer. The drug is associated with minimal side-effects and only 10% (18/186) had to discontinue treatment because of these effects. Initially the intramuscular injection was seen as a potential disadvantage, but once a reduced dose was established as being effective, the injections were tolerated well, with only 4/96 (4%) of patients receiving 250 mg every 2 weeks having to discontinue treatment. Other side-effects, seen with aminoglutethimide, such as drowsiness and ataxia, and evidence of corticosteroid synthesis inhibition were never seen, since no changes of electrolytes or serum cortisol, attributable to 4OHA were observed in patients in our studies. A more extensive study, an endocrine and pharmacokinetic study of four oral doses of 4-OH-androstenedione in postmenopausal breast cancer patients confirms that 4-OH-androstenedione has no effect on serum cortisol) [9]. When aminoglutethimide is given alone, a dose-related increase in serum levels of androstenedione is seen. No such increases were seen with either the 250 or 500 mg doses given twice weekly. Similarly, other common side-effects of frequently-used second-line endocrine therapies, such as weight gain, cushingoid faces and tumour flare were never seen. Hirsutes, attributable to 4OHA, was only seen in one of the patients.

The drug also appears to have benefit over other newer aromatase inhibitors. Thus, pyridoglutethimide causes CNS side-effects [10] and CGS16949 causes inhibition of aldosterone synthesis, which has never been seen with 4OHA [9].

A further advantage of 4OHA over pyridoglutethimide and aminoglutethimide is that the latter two compounds have been shown to induce their own metabolism with repeated administration. At a dose of 250 mg the drug shows an effective concentration following the first injection and steady state conditions are reached after four injections, as reflected by sustained oestrogen suppression. No accumulation of 4OHA has been consistently demonstrated, presumably due to the constant excretion of 4OHA by the kidney and bile after glucuronidation [1].

The pharmacokinetics of 4OHA indicate that there is a depot formed at the site of injection which continues to release the drug over a 2-week period. This almost certainly is the major factor in the prolonged duration of the oestrogen suppressive effect of intramuscularly-administered drug. There was a small degree of recovery of serum oestradiol levels shown just prior to the 2-weekly injection of 4OHA for the 250 mg dose which was not apparent with the 500 mg dose. In isolation this observation would argue for the use of the higher dose. However, the marginal nature of this recovery, the good response rate with the 250 mg dose and the greater incidence of local side-effects with the 500 mg dose, indicates that 250 mg every 2 weeks is the dose of choice. Other endocrine analyses currently indicate that when 4OHA is given by the intramuscular route it is a 'pure' aromatase inhibitor which lacks any significant inherent androgenic or oestrogenic activity.

Which patients appear to benefit most from 4OHA therapy? Patients who have responded previously to endocrine therapy appear to do well, as do patients who have oestrogen receptor positive carcinomas and one or, at most, two sites of metastases also appear to do well. As with all endocrine therapies, patients with liver metastases do not appear to benefit from treatment. What other potential applications may there be? Studies by our group have demonstrated that premenopausal patients, after having achieved a remission with LHRH agonists, can achieve

a second response with the addition of 4OHA to LHRH agonist therapy [11]. We have also shown that 4OHA is effective in primary breast cancer and acceptable as adjuvant therapy over 18 months given as 250 mg intramuscularly every 2 weeks [12].

Future studies need to determine whether 40HA, when used following tamoxifen therapy, is of value in extending survival in patients with primary breast cancer.

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Variations in Breast Cancer Management Between a Teaching and a Non-teaching District

Ian Basnett, Mike Gill and Jeffrey S. Tobias

We compared the management and outcome of 999 women with breast cancer presenting between 1982 and 1986 at two centres in a region, one in a teaching district. A comparison was also made with relevant research and The Kings Fund Consensus Statement. The centres frequently differed markedly in the investigations done, diagnostic procedures, histology reporting, axillary sampling, and in the treatment given, also differing from the Consensus with no trend towards it. Survival was better at the teaching centre, both disease-free (N.S.) and overall [odds ratio 1.46 (1.16–1.84) $P = 0.0009$ unadjusted]. This should be interpreted cautiously as the median follow-up time was relatively short and the study was non-randomised. We conclude that how women with breast cancer are managed is determined as much by where they are referred as by scientific evidence. This indicates the need to introduce standards and protocols into business plans, making audit and service specifications easier.
Eur J Cancer, Vol. 28A, No. 12, pp. 1945–1950, 1992.

INTRODUCTION

MANY PREVIOUS studies have documented variations in both management and outcome in a variety of cancers [1–5]. Such differences clearly raise questions about both the cost and effectiveness of the treatment. In breast cancer doubts persist about the best forms of management. However, there are some areas where established standards do exist and departures from them are of interest.

We compared the management and outcome of women with breast cancer at two centres where radiotherapy and chemotherapy were available, one in an urban teaching district (T) comprising two hospitals, the other a rural non-teaching district, some 60 miles away (NT). The null hypothesis was that there would be no difference between them. We used accepted research and consensus statements as benchmarks for comparison. The King's Fund consensus conference [6] is the most

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