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4-HYDROXYANDROSTENEDIONE TREATMENT FOR POSTMENOPAUSAL PATIENTS WITH BREAST CANCER

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Summary—Patients (186) with locally advanced or metastatic breast cancer were treated with the aromatase inhibitor 4-hydroxyandrostenedione given parenterally at 3 different doses. 21% of patients responded to treatment, 93% of objective responders whose oestrogen receptor (ER) status was known had ER positive tumours. The drug was well-tolerated particularly at a dose of 250 mg i.m. every fortnight. At this dose, only 4/96 (4%) patients had to discontinue treatment. We conclude that 4-hydroxyandrostenedione is a well-tolerated form of endocrine treatment for postmenopausal patients with breast cancer.

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, almost 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 sedatory effects nor the other non-specific enzyme inhibitory effects of aminoglutethimide.

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

PATIENTS AND METHODS

Patients

Details of the patients studied are shown in Table 1. Patients (186) received one of three doses; 500 mg i.m. weekly (61 patients); 500 mg i.m. every 2 weeks (29 patients), and 250 mg i.m. 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. Thirty four 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 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

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

	Dose/schedule		
	500 mg i m weekly	500 mg i.m. fortnightly	250 mg i m fortnightly
No.	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%)

clinical examination and measurement of all measurable lesions. Assessment of response was according to Hayward *et al.* [5]. 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 one month apart. The "no change" category referred to patients whose disease had stabilized for at least this period of time.

Results of treatment

Table 2 reviews the results obtained in the 3 dose schedules used for all evaluable patients and for patients who completed at least 4 weeks' treatment. Nineteen patients (10%) were not considered evaluable for response because of concomitant anti-cancer 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 21% and not significantly different between the three groups. Table 3 shows the minimum, maximum and median duration of response to the 3 dose schedules. No significant difference is seen.

A major determinant of response was the ER status of the primary or recurrent tumour. Thus, 13/14 (93%) objective responders whose oestrogen receptor (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. 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

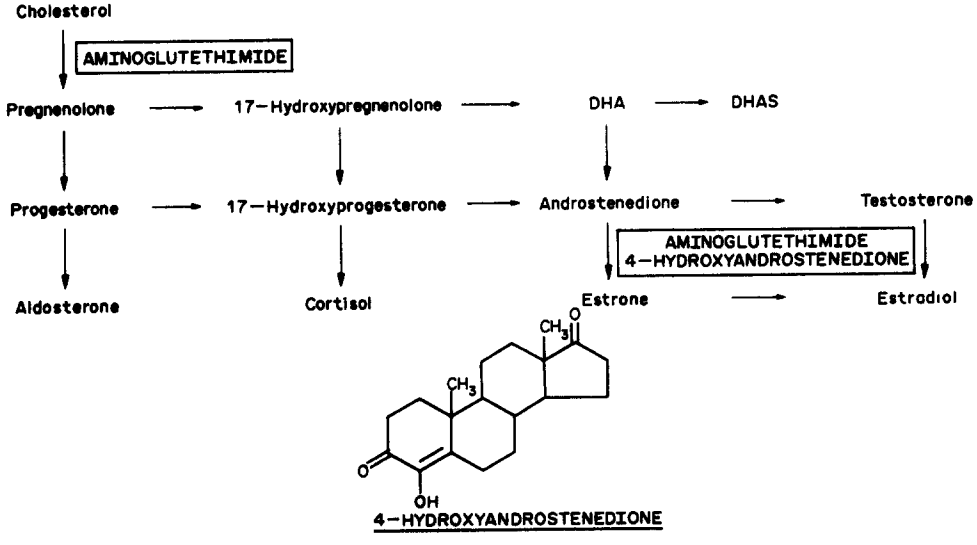

Fig. 1. Sites of steroid synthesis inhibition by aminoglutethimide and 4-OHA. This figure also shows the structure of 4-OHA.

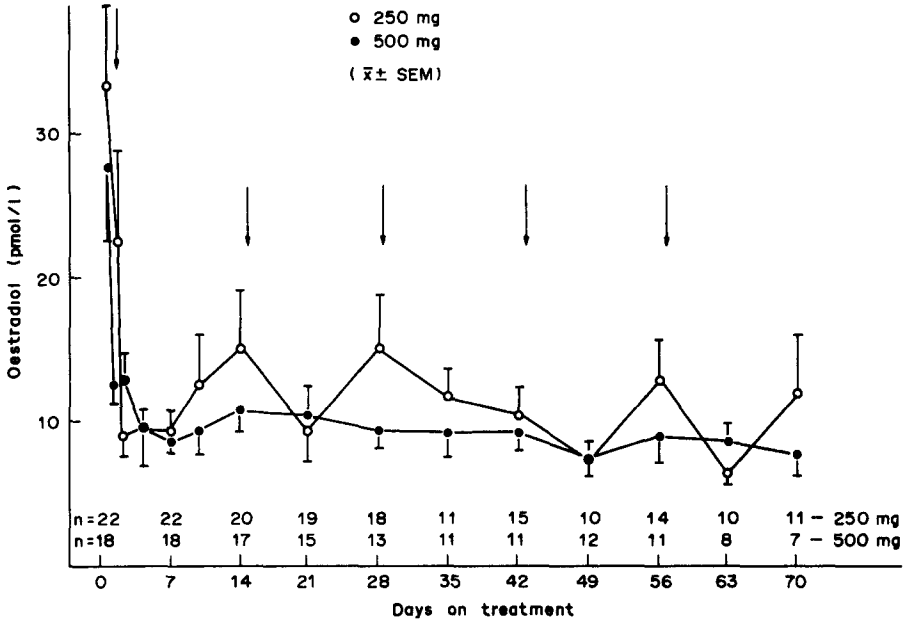

Fig. 2. Serum oestradiol levels (±SEM) following treatment with either 4-OHA 250 mg i.m. fortnightly (○) or 500 mg i.m. fortnightly (●). Arrows indicate time of injections.

Table 2. 4-OHA results of treatment

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

[a]See text for reasons for non-evaluability.

(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%

Table 3. Parental 4-OHA study: duration of response (days) for patients who responded (CR, PR) or stabilized (NC) on treatment

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

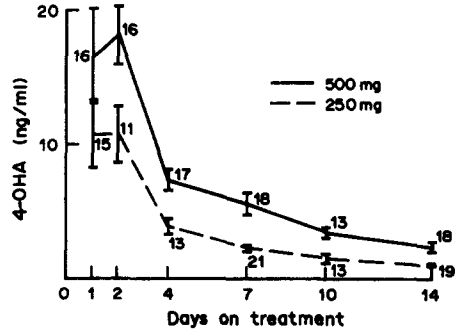

Fig. 3. Serum 4-OHA in postmenopausal patients with breast cancer (±SEM). The solid bar indicates the levels after a single injection of 500 mg and the interrupted bar indicates the levels after a single injection of 250 mg.

Table 4. 4-OHA: side effects of therapy

	Dose/schedule		
	500 mg i m weekly	500 mg i m. fortnightly	250 mg i.m fortnightly
No	61	29	96
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

of patients complained of local side effects, principally pain and/or inflammation at the site of injection. Other side effects included an anaphylactoid reaction in 5 patients, presumably due to inadvertent i.v. administration in some cases which could be avoided by greater care with i.m. administration 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.

CONCLUSION

These studies show that 4-OHA 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 i.m. 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 i.m. 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 4-OHA were observed in patients in our studies. 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 4-OHA, was only seen in a single patient treated.

The drug also appears to have benefit over other newer aromatase inhibitors. Thus, pyridoglutethimide causes CNS side-effects [6] and CGS16949 causes inhibition of aldosterone synthesis, which has never been seen with 4-OHA [7].

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