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Aminoglutethimide Dose and Hormone Suppression in Advanced Breast Cancer

A. L. HARRIS,* M. DOWSETT,† S. L. JEFFCOATE† and I. E. SMITH*

Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3, U.K. and †Department of Endocrinology, Chelsea Hospital for Women, Dovehouse Street, London SW3, U.K.

Abstract—*The effect of the dose of aminoglutethimide on the suppression of oestrone, oestradiol and dehydroepiandrosterone sulphate (DHAS) levels was studied in 36 women with advanced postmenopausal breast cancer, all of whom received 20 mg hydrocortisone twice daily as replacement glucocorticoid. Aminoglutethimide (AG) 250 mg twice a day was as effective as AG 250 mg 3 times a day or AG 250 mg 4 times a day. Side-effects were less at the lowest dosage and were age-related. On-treatment oestrone levels were higher in non-responders to treatment. Lower doses of AG than are currently used may be as effective therapeutically.*

INTRODUCTION

AMINOGLUTETHIMIDE is an inhibitor of adrenal steroidogenesis, acting on the 20,22 desmolase, which catalyses the conversion of cholesterol to pregnenolone [1]. Hydrocortisone in replacement doses is usually given with aminoglutethimide to prevent a secondary rise in ACTH which might overcome the enzyme block [2]. When given in this combination aminoglutethimide has been found to be an effective treatment of advanced postmenopausal breast cancer [3], achieving response rates similar to tamoxifen [4]. As well as the adrenal suppression achieved by the aminoglutethimide/hydrocortisone combination, aminoglutethimide inhibits the conversion of androgens to oestrogens which is catalyzed by the aromatase enzyme system in peripheral tissues [5].

Conventional doses of aminoglutethimide (i.e. 1 g per day in 4 divided doses) are associated with side-effects in 41.5% of patients [3]. In our earlier series of 213 patients [6] 5% had to discontinue the drug, 9.5% reduced the dose and 33% had side-effects. This current drug regimen was designed to inhibit adrenal steroid synthesis and thus achieve a so-called 'medical adrenalectomy'. However, the aromatase enzyme system is much more sensitive than the desmolase to inhibition by aminoglutethimide when tested *in vitro* [7]. It is therefore possible that doses of aminoglutethimide lower than those conventionally used could achieve as effective a suppression of patient oestrogen levels as do the higher doses. We have carried out a dosage study with aminoglutethimide to examine this possibility and to see if lower doses are associated with a lower frequency of side-effects. We also assessed the relationship between the degree of hormone suppression achieved and progression or regression of disease.

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MATERIALS AND METHODS

Patients

Thirty-six patients with advanced postmenopausal breast cancer were studied. Ages ranged from 29 to 76 yr (median 55.5 yr), time from last menstrual period 1–26 yr (median 9.5 yr) and the tumour-free interval 0–156 months (median 19 months). Twenty-four patients had received previous endocrine therapy, which produced the following responses: 9 partial responses, 3 disease stabilisations for more than 6 months, 9 progressive disease and 3 non-evaluable responses. Six patients had previously had oophorectomies (ages 29–50 at the time of this study).

The first 24 patients were given aminoglutethimide 250 mg 3 times a day (t.d.s.) for 2 weeks. Dosage was then increased to 250 mg 4 times a day (q.d.s.). Patients were told to take the first and third doses 12 hr apart, at 8 a.m. and 8 p.m. The second dose was taken at lunch time and the fourth before going to bed. The following 12 patients were given 250 mg of aminoglutethimide twice a day (8 a.m. and 8 p.m.) for 2 weeks. The

dose was then increased to 250 mg t.d.s. for 2 weeks and thence to q.d.s. All patients received hydrocortisone 20 mg 12-hourly throughout this treatment. There were 2 oophorectomised patients in the group starting on aminoglutethimide 250 mg twice a day and 4 oophorectomised patients in the group starting on aminoglutethimide 250 mg 3 times a day.

Patients were maintained on the maximum tolerated dose of aminoglutethimide until disease progressed. Response was assessed by standard IUCC criteria [8].

Methods

Blood samples were taken before treatment and at 2-week intervals, between 9.30 and 11.00 a.m. and the resulting serum was stored at -20°C until analysis. Dehydroepiandrosterone sulphate (DHAS) was assayed by radioimmunoassay in serum diluted ×100 as described previously [9].

The radioimmunoassays for oestrone and oestradiol were carried out in ether extracts of serum. Recovery was found to be greater than 90% in all tests and therefore a recovery control was not routinely instituted. The oestrone assay used an antiserum kindly donated by Dr. J. Moore, I.C.R.F. The antiserum was raised against a C-6-linked immunogen and had the following cross-reactions calculated at the level of 50% displacement of bound labelled hormone: 2-hydroxyoestrone 0.19%, 16α-hydroxyoestrone 0.19%, 2-methoxyoestrone 0.11%, all others, including 17β-oestradiol, <0.05%. [2,4,6,7-^{3}H]-Oestrone (Amersham International) was used as tracer label. The within- and between-assay coefficients of variation (CVs) were 6.8 and 10.7% respectively at a plasma concentration of 120 pmol/l. The lower limit of sensitivity of the assay was 30 pmol/l. The oestradiol assay used antiserum and tracer obtained from the Swiss Federal Reactor Institute, the tracer being [^{125}I]-histamine-6-CMO-oestradiol. The cross-reactions calculated as above were: oestriol 1.8%, oestrone 0.03%, all others <0.03%. The within- and between-assay CVs were 6.7 and 12.0% respectively at a plasma concentration of 25 pmol/l. The lower limit of sensitivity was 6 pmol/l.

Side-effects

At each clinic attendance patients were specifically asked to recall instances of drowsiness, nausea, depression, rashes and 'dizziness'. They were asked to describe any other side-effects. Symptoms were recorded as persistent if they did not subside within 2 weeks of onset. In these circumstances aminoglutethimide dosage was not increased.

RESULTS

Hormone suppression and aminoglutethimide dose

The combination of aminoglutethimide and hydrocortisone significantly suppressed DHAS, oestrone and oestradiol at each dose level ($P<0.01$) (Fig. 1). There was no significant difference between the hormone levels found at the 3 doses of aminoglutethimide, and similarly, there was no significant difference in the percentage suppression achieved by the 3 doses (unpaired t tests, $P>0.10$) (Figs 1 and 2). The results in Figs 1 and 2 are for all patients who received the stated aminoglutethimide dose. Thus the results for aminoglutethimide 250 mg 3 times a day include 12 patients who started on aminoglutethimide 250 mg twice a day (b.d.) and increased to 3 times a day, as well as the 24 patients who started on aminoglutethimide 250 mg 3 times a day.

One month after starting treatment the patients who started at 250 mg aminoglutethimide b.d. had only been taking aminoglutethimide 250 mg t.d.s. for 2 weeks, whilst the patients who started at 250 mg t.d.s. had been on this dose or greater for the whole month. To examine the possibility that this variability could cause differences in hormone suppression the hormone values have been compared at 2 and 4 weeks by paired t tests for each cohort of patients and by unpaired t tests

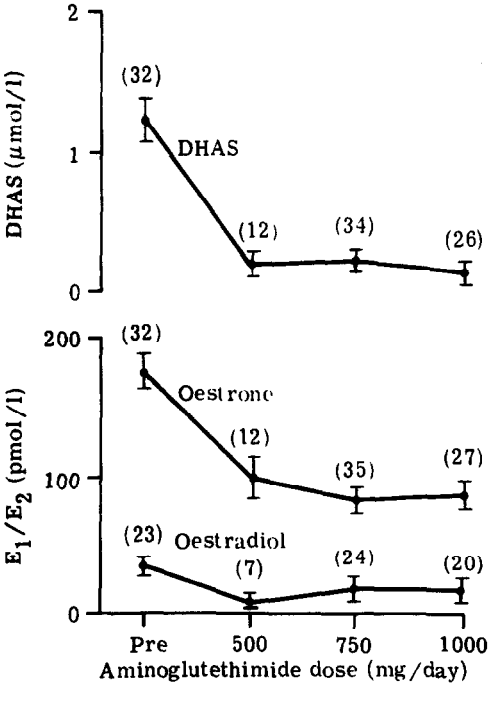

Fig. 1. Hormone levels before treatment and while receiving aminoglutethimide 250 mg *b.d.,* 250 mg *t.d.s. and* 250 mg *q.d.s. Bars show S.E.M. Figures in parentheses are Nos of patients at each dose level.*

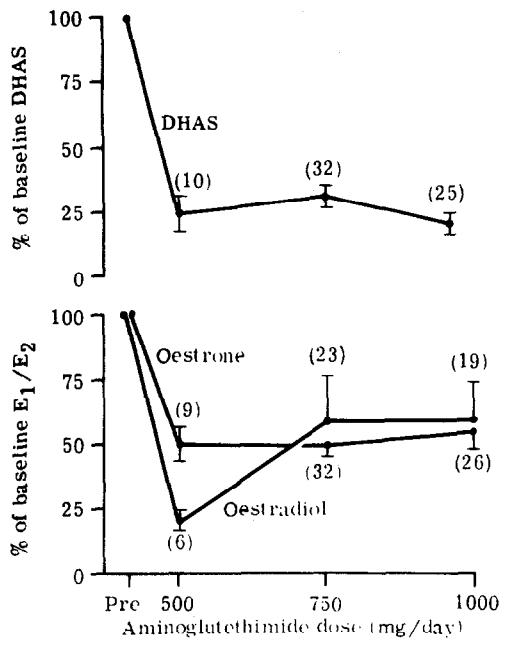

Fig. 2. Hormone suppression expressed as % of baseline values in patients treated with aminoglutethimide 250 mg *b.d.*, 250 mg *t.d.s. and* 250 mg *q.d.s. Bars show S.E.M. Figures in parentheses are Nos of patients at each dose level.*

between the cohorts (Table 1). There was no significant difference in oestrone or oestradiol suppression at either time period or any of the doses. There was a further small fall in DHAS at 1 month in both groups of patients, which was significant only in the group starting at aminoglutethimide 250 mg t.d.s. ($P<0.001$). Thus aminoglutethimide 250 mg b.d. was as effective as 250 mg q.d.s. in suppressing oestrone, oestradiol and DHAS.

Side-effects and aminoglutethimide dose

In an analysis of frequency of side-effects, patients with one or more side-effects were counted once. As the dose increased, the percentage of patients with side-effects requiring dose reduction or stopping of treatment increased (Table 2). Twelve of thirty-six (33%) patients receiving more than 250 mg b.d. of aminoglutethimide did not tolerate full dosage. In these patients side-effects were age-related. Three of four patients greater than 71 yr old (75%), 5/8 patients aged 61–70 yr (62.5%), 3/14 patients aged 51–60 yr (21.4%) and 1/10 patients less than 50 yr old (10%) did not tolerate the full dose (χ^2, $P<0.05$). At the lowest dose there were two cases of transient side-effects. Both of these were rashes; none of the patients at this dosage had drowsiness, nausea or dizziness.

Response and hormone suppression

Response to therapy was as follows: objective response, 12 patients; progressive disease, 22 patients; non-assessable (because of excision of local recurrence), 2 patients. There was a significant excess of non-responders having an oestrone level greater than 120 pmol/l whilst on therapy ($P<0.05$) (Fig. 3). There was no difference in years from the last menstrual period, in tumour-free interval or in age to explain these high oestrone levels. However, 5 of the 6 patients with oestrone >120 pmol/l had bulky liver secondaries, whilst only 1 of 24 patients without liver secondaries had an oestrone level <120 pmol/l ($P<0.01$). There was no difference in DHAS suppression (Table 3).

DISCUSSION

The side-effects of aminoglutethimide are a limiting factor in the use of the drug, which has been found to be effective in tamoxifen-resistant patients [4] and also appears to be particularly effective in bone secondaries [4, 6, 10]. This study shows that doses of 250 mg b.d. are as effective as 250 mg q.d.s. in producing oestrone suppression, whilst side-effects are less at the lower dose.

Table 1. Hormone concentrations on treatment with aminoglutethimide

Treatment at time of sample	Length of time on treatment at time of sample (weeks)	Oestrone: mean (pmol/l) S.E.M.	Oestradiol: mean (pmol/l) S.E.M.	DHA-S: mean (μmol/l) S.E.M.
AG 2× per day	2	100	7	0.34
		12	1.5	0.07
AG 2× per day	4	84	7	0.25
3× per day		9	1	0.04
AG 3× per day	2	80	19	*0.44
		11	6	0.06
AG 3× per day	4	87	21	*0.29
4× per day		12	5	0.05

*Significant fall in DHA-S between 2 and 4 weeks ($P<0.001$).

Table 2. Side-effects and dose modifications of aminoglutethimide in 36 patients receiving increasing doses of aminoglutethimide

Aminoglutethimide dose	No. of patients	No. without side-effects (%)	No. with transient side-effects (%)	No. with persistent side-effects (%)	No. reducing dose (%)	No. stopping (%)
250 mg 2× per day	12	9 (75)	2 (16.7)	1 (8.3)	0	0
250 mg 3× per day	36	22 (61.1)	8 (22.2)	3 (8.3)	1 (2.8)	2 (5.5)
250 mg 4× per day	30	19 (63.3)	5 (16.7)	0	3 (9.7)	3 (9.7)

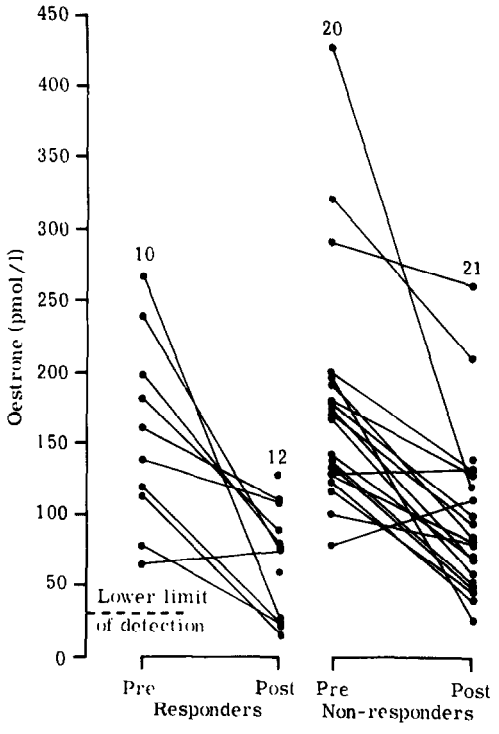

Fig. 3. Plasma levels of oestrone before and after treatment with aminoglutethimide at the maximally tolerated dose. Responders had objective response of advanced breast carcinoma.

There was no further suppression of oestrone with increasing aminoglutethimide dose in individual patients. This suggests that current doses are at the top of a dose–response curve for hormone suppression. Since aminoglutethimide has a dual site of action it is possible that oestrone suppression is produced mainly by peripheral aromatase inhibition rather than by suppression of adrenal steroidogenesis, and that the larger doses which are required to induce the latter are not necessary therapeutically.

The further small fall in DHAS at 4 weeks has been previously found by Samojlik *et al.* [11] and by Murray *et al.* [12] in patients who were not receiving increasing doses of aminoglutethimide. This may be due to the long half-life of DHAS rather than any effect of the increase in aminoglutethimide dose.

It has been noted that aminoglutethimide induces its own metabolism [13]. Thus the increased dosage at 2 weeks may be maintaining plasma levels of aminoglutethimide that had been reduced by liver metabolism, and hence this could be a reason for the lack of further oestrone suppression. This is, however, unlikely as there was no difference in oestrone levels at 2 weeks in those patients starting on 250 mg b.d. or 250 mg t.d.s. Furthermore, side-effects increased with dosage and decreased when dosage was reduced. The induction probably occurs within 1 week of

Table 3. Hormone levels and % of baseline values in 34 patients while receiving aminoglutethimide at maximal tolerated dose

	Responders			Non-responders		
	Mean	S.E.M.	(*n*)	Mean	S.E.M.	(*n*)
Oestrone (pmol/l)	70.4	10.1	(12)	98.8	12.2	(21)
% of baseline	48.5	9.8	(10)	56.8	6.4	(20)
Oestradiol (pmol/l)	11.9	3.7	(9)	18.8	5.0	(13)
% of baseline	35.8	7.7	(8)	69.9	6.5	(13)
DHAS (μmol/l)	0.3	0.08	(12)	0.27	0.04	(20)
% of baseline	21.3	5.3	(11)	26.6	5.3	(17)

starting therapy, since Murray *et al.* [13] found no difference in aminoglutethimide plasma levels from 1–12 weeks after starting aminoglutethimide. It is possible that our observation of increased incidence of side-effects with age may also be related to plasma aminoglutethimide levels, if metabolism is slower in elderly patients.

Santen *et al.* [10] found higher DHAS in non-responders and this may be a non-specific response to stress. We found no difference in DHAS, but there was a subgroup of patients with high oestrone levels. Since we have shown that increasing dosage of aminoglutethimide does not suppress oestrone further, it is unlikely that this is due to resistance to the effects of aminoglutethimide. The association with bulky liver disease suggests that these high levels may be due to decreased clearance of steroids by the diseased liver. We are investigating this possibility with infusion studies. This may partly explain the poor response of liver secondaries to endocrine therapy, although they are often oestrogen receptor positive [14].

Although hormone suppression is the same on aminoglutethimide 250 mg b.d. as on 250 mg q.d.s., the design of this study did not permit assessment of tumour response at the lowest dose level. Paridaens *et al.* [15] has observed responses at 250 mg b.d., and in a series of 190 patients, 18 who received 250 mg t.d.s. had the same response rate as those receiving 250 mg q.d.s. [6].

As a result of these studies we feel that it is now justifiable to assess lower-dose aminoglutethimide in a controlled trial vs conventional-dose aminoglutethimide. The lower dose may also be used in combination endocrine therapy and improve compliance. We have initiated such trials.

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