Eur J Cancer, Vol. 27, No. 7, pp. 846–849, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Low-dose Aminoglutethimide in Postmenopausal Breast Cancer: Effects on Adrenal and Thyroid Hormone Secretion

M. Dowsett, A. Mehta, B.M.J. Cantwell and A.L. Harris

Aminoglutethimide is effective in the treatment of breast cancer in postmenopausal patients as a result of its inhibition of aromatase. Its use is complicated by a number of endocrine side-effects which include the inhibition of thyroxine synthesis and inhibition of 11-steroid and 21-steroid hydroxylases. When aminoglutethimide is used at the conventional daily dose of 1000 mg in combination with 40 mg of hydrocortisone these effects can result in clinically significant hypothyroidism and increases in the serum levels of oestrone in response to stimulation of adrenocorticotropic hormone (ACTH). In the current study it was found that with twice daily treatment at the low dose of 125 mg aminoglutethimide plus 20 mg hydrocortisone there was no significant increase in oestrone levels after ACTH stimulation. In addition there was little effect on thyroid function: serum levels of triiodothyronine and thyroxine were unaffected whilst there was a marginally significant ($P < 0.05$) increase in thyroid-stimulating hormone (TSH) levels from a mean (S.E.) 2.37 (0.23) mU/l to 3.78 (1.23) mU/l. The increased TSH levels were confined to those patients with pretreatment values greater than 2.5 mU/L, the most marked effect being in 1 patient whose pretreatment level was already outside the normal range.
Eur J Cancer, Vol. 27, No. 7, pp. 846–849, 1991

INTRODUCTION

AMINOGLUTETHIMIDE is a clinically effective treatment for postmenopausal breast cancer as a result of its suppression of oestrogen synthesis [1, 2]. It was considered for many years that aminoglutethimide was clinically effective in breast cancer by acting as a suppressant of adrenal steroid secretion as a result of its inhibition of 20, 22 desmolase, the enzyme that catalyses the conversion of cholesterol to pregnenolone [3, 4]. However, extensive endocrine investigations have demonstrated that aminoglutethimide inhibits numerous other cytochrome P450 dependent steroid hydroxylases [5, 6] and it is now accepted that it is by aromatase inhibition that the suppression of postmenopausal oestrogen synthesis is achieved [1, 7].

Indeed, rather than suppressing adrenal androgen secretion the overall effect of aminoglutethimide on adrenal steroid secretion is detrimental to the aim of oestrogen suppression. The inhibition by the drug of 11-hydroxylases and 21-hydroxylases leads to dose-related increases in the circulating levels of 17α-hydroxyprogesterone, androstenedione and testosterone, the latter two androgens being immediate precursors of oestrone and oestradiol, respectively [7, 8]. The effect of these enzyme blocks on cortisol synthesis has led to the use of aminoglutethimide in combination with hydrocortisone. This reduces, but does not obliterate, the effects of aminoglutethimide on androgen levels [9]. Most importantly, and possibly in relation to the effects on androgen levels, it has been found that patients on the conventional dose of aminoglutethimide (1000 mg/day) plus hydrocortisone respond to stimulation of adrenocorticotropic hormone (ACTH) by an increase in oestrone levels [10]. The frequent occurrence of stressful situations in the postmenopausal breast cancer patient may thus lead to suboptimal oestrogen suppression as a result of these other enzyme blocks. The other clinically important endocrine complication with aminoglutethimide is its effect on thyroxine secretion: many patients on conventional doses of aminoglutethimide show raised thyroid-stimulating hormone (TSH) levels indicating a subclinical hypothyroidism in some patients and overt hypothyroidism in some [11, 12].

We have previously demonstrated that low-dose aminoglutethimide (125 mg twice daily) plus hydrocortisone appears to have comparable clinical efficacy to the conventional dose whilst the side-effects appear to be reduced, although randomised comparative trials have yet to be conducted [13]. The oestrogen suppressive effects of the low dose are not significantly different from the conventional dose, but the stimulatory effects on androgen secretion are much reduced [7]. In this report we examine whether this dose reduction has additional benefits with regard to reducing the effects of aminoglutethimide on ACTH-stimulated increases in oestrogen levels and the secretion of thyroxine.

PATIENTS AND METHODS

Patients

All patients were postmenopausal (spontaneous or therapeutic) and had advanced breast cancer. Treatment was 125 mg aminoglutethimide and 20 mg hydrocortisone, both twice daily.

Synacthen tests were performed on 12 patients after a mean (S.D.) 35.8 (25.5) weeks treatment (range 8–90). The mean age of these patients was 58.1 (9.7) years and their mean weight was 60.8 (9.5) kg. Synacthen (250 μg) was given as an intramuscular injection between 11.00 and 15.00 and blood samples were

Correspondence to M. Dowsett.
M. Dowsett and A. Mehta are at the Department of Biochemical Endocrinology, Royal Marsden Hospital, Fulham Road, London, SW3 6JJ; B.M.J. Cantwell is at the University Department of Clinical Oncology, Regional Radiotherapy Centre, Newcastle General Hospital, Newcastle; and A.L. Harris is at the ICRF, Clinical Oncology Unit, Churchill Hospital, Oxford, U.K.
Received 7 Mar. 1989; accepted 9 Apr. 1991.

collected before and at 30 minute intervals after injection for 2 h.

Thyroid function tests were performed on 33 patients before and 13.2 (11.0) weeks after starting treatment range (2–60 weeks). 4 of these were in the group receiving a Synacthen test. The mean age and weight of the 33 were 61.2 (11.8) years and 59.8 (10.7) kg, respectively.

Assays

All samples of serum were stored at −20°C until analysis. All samples from the same patient were analysed in the same assay batch. Samples from the Synacthen test were analysed for 17α-hydroxyprogesterone [14], androstenedione [15], oestrone [16] and oestradiol [17] by radioimmunoassays. Cortisol levels were measured using the Biogenesis direct radioimmunoassay kit. The assays for thyroxine (T4) and triiodothyronine (T3) and TSH were conducted with Amerlex kits (Amersham International). The within and between assay coefficients of variation were < 7% and < 10%, respectively, for all assays.

RESULTS

The mean (S.E.) pre-Synacthen levels of cortisol, oestradiol, oestrone, androstenedione and 17α-hydroxyprogesterone were 516 (134) nmol/l, 5.2 (0.6) pmol/l, 43.2 (6.2) pmol/l, 1.1 (0.3) nmol/l and 3.6 (0.4) nmol/l, respectively.

The mean changes in each of the five parameters after the Synacthen tests are shown in Fig. 1. For each of the hormones the effects at 30 minutes were maintained largely unchanged for the next 90 minutes. Cortisol levels and oestradiol levels were unaffected by the Synacthen treatment, and although the mean levels of oestrone were above the pre-Synacthen sample at each time point after the injection, in no case was this statistically significant. This was despite significant increases in the levels of androstenedione (about 1.5 nmol/l) and of 17α-hydroxyprogesterone (about 12 nmol/l).

Although there were no statistically significant changes in mean oestrogen levels, in 1 patient oestrone levels increased

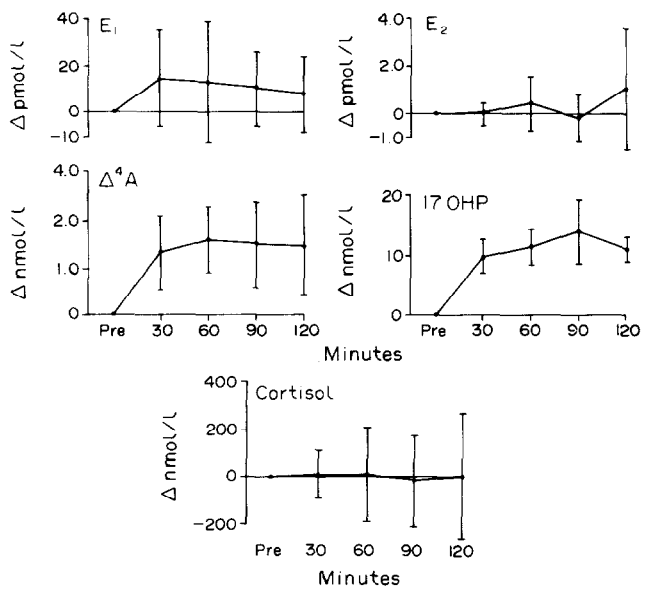

Fig. 1. Mean change (95% confidence limits) in serum levels of oestrone (E_1), oestradiol (E_2), androstenedione (Δ^4A), 17α-hydroxyprogesterone (17OHP) and cortisol after 250 μg injection of Synacthen in 12 patients on 125 mg aminoglutethimide + 20 mg hydrocortisone, both twice daily.

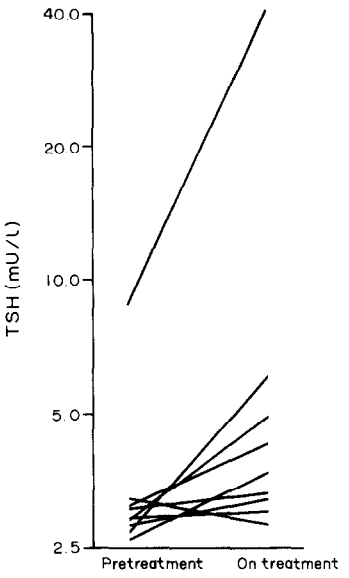

Fig. 2. Changes in serum levels of TSH in 9 patients on 125 mg aminoglutethimide + 20 mg hydrocortisone both twice daily in whom pretreatment value was over 2.5 mU/l.

from 43 pmol/l pre-injection to 107, 127, 100 and 80 pmol/l at the 30, 60, 90 and 120 postinjection time points, respectively. This patient had the most marked Synacthen-induced increase in androstenedione levels (change of 4.4 nmol/l) and one of the larger increases in 17α-hydroxyprogesterone levels (change of 18 nmol/l).

The mean pretreatment (S.E.) levels of T3 and T4 before treatment were 1.95 (0.17) and 119 (6) nmol/l and during treatment were 1.74 (0.09) and 115 (5) nmol/l respectively. The on-treatment levels were not significantly different from those before treatment. There was, however, a marginally significant increase in TSH levels: pretreatment, 2.37 (0.23) mU/l; on treatment, 3.78 (1.23) mU/l (Wilcoxon matched-pairs signed-ranks test, $P < 0.05$). The increase was confined largely to the 9 patients with pretreatment levels over 2.5 mU/l (Fig. 2), 8 of the 9 showing increased levels. In 1 patient there was an increase from 8.8 to 41.6 mU/l during treatment despite there being no marked change in T3 (1.47 to 1.18 nmol/l) or T4 (95 to 94 nmol/l) levels. The mean levels before and during treatment in the group with pretreatment levels of TSH of ≤ 2.5 mU/l were 1.90 (0.07) and 2.09 (0.16) mU/l, respectively.

DISCUSSION

Aromatase inhibition was first demonstrated to be an effective mode of treatment in postmenopausal breast cancer by the use of aminoglutethimide [18]. The clinically significant side-effects of aminoglutethimide and its lack of specificity have led to the search for new aromatase inhibitors, a number of which have now reached early phase clinical trials [19, 20]. In the meantime we have taken the route of examining lower dosages of aminoglutethimide as an approach to achieving aromatase inhibition with an improved clinical and pharmacological profile. Through a series of studies we determined that 125 mg aminoglutethimide twice a day was the minimum dose to achieve maximal suppression of oestrogen levels [7, 8]. It was also found that aminoglutethimide at this low dose had to be combined with hydrocortisone for maximal effectiveness in oestrogen suppression [21] and this has recently been confirmed by others [22]. The major clinical side-effects of aminoglutethimide, other

than the associated rash, appear to be less frequent with the low dose, whilst the response rate appears to be similar to high dose aminoglutethimide [13] although formal comparative trials have yet to be conducted. The observations in the current study also indicate that two of the endocrine side-effects of aminoglutethimide are less apparent at the low dose.

It has been known for many years that aminoglutethimide inhibits thyroxine synthesis and may cause goitrous hypothyroidism in both children and adults [11, 12, 23]. Santen *et al.* [11] found that patients receiving 250 mg aminoglutethimide four times daily had significantly decreased thyroxine levels (by a mean 18% over the first 8 weeks treatment) but in only 2/35 were thyroxine levels below the reference range. The decrease was associated with a marked (approximately 2-fold) and highly significant increase in TSH levels, which resulted in values outside the normal range in 50% of patients. A more severe pattern of aminoglutethimide-induced hypothyroidism was noted by Bruning *et al.* [12].

It is clear that in the current study the effects on thyroid function with low dose aminoglutethimide were far less marked. The 1 patient that had a highly abnormal TSH level on treatment already had a marginally abnormal level (> 8 mU/l) before treatment. Even in this patient, T4 and T3 levels were not abnormally low. Whilst the increase in TSH levels in 8 of 9 patients with pretreatment values > 2.5 mU/l indicates that low-dose aminoglutethimide may have a minor effect on thyroxine synthesis, it appears that this is unlikely to be of clinical significance in all but the most extreme circumstances.

Bruning *et al.* [10] reported oestrone levels to be significantly increased 120 minutes after 500 μg Synacthen injection in patients on 250 mg aminoglutethimide four times daily + 40 mg hydrocortisone daily (10 +10 + 20 mg), the mean increase being about 20 pmol/l. In our earlier study of patients on the same doses of aminoglutethimide and hydrocortisone [7] we were unable to confirm the change in oestrone levels, but measurements were made after only 30 minutes. In the current study measurements were made for 2 hours after Synacthen. Although increases in 17α-hydroxyprogesterone and androstenedione levels were seen these were less than half of those observed in our study of high-dose aminoglutethimide and we were once again unable to confirm a significant increase in oestrone levels.

Any increase in oestrone levels after Synacthen suggests that the increased levels of its precursor (androstenedione) which result from the inhibition of glucocorticoid synthesis are sufficient to partially overcome the aminoglutethimide-induced block of aromatisation. We have previously shown that there is little difference between the inhibition of aromatisation with the high and low doses [24]. Thus the greater increase in androstenedione levels resulting from Synacthen stimulation in the higher dose patients may be instrumental in eliciting the increase in oestrone levels, as observed by Bruning *et al.* [10]. Alternative possible explanations for this discrepancy between the two studies are the use of a higher dose (500 μg) of Synacthen by Bruning *et al.* and that patients in the two studies may have differed in their response to aminoglutethimide and Synacthen. There is evidence in the current study that 1 of our patients showed an increase in oestrone levels, and the mean levels after Synacthen were increased but the effect lacked statistical significance. Both studies had relatively small numbers such that a minor difference in the numbers of patients showing an oestrogenic response to Synacthen could markedly alter the mean results.

In conclusion, there is no evidence that stress in patients treated with low dose aminoglutethimide plus hydrocortisone is more likely to cause increases in oestrogen levels than during high dose treatment. On the contrary, the evidence in the current report suggests that this is less likely to occur. The lower incidence of inhibitory effects on thyroxine synthesis with the low dose, strengthens the case for 125 mg aminoglutethimide twice daily being selected as the optimum dose for breast cancer treatment.

1. Santen RJ, Santner S, Davis B, Veldhuis J, Samojlik E, Ruby E. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. *J Clin Endocrinol Metab* 1978, **47**, 1257–1265.
2. Harris AL, Powles TJ, Smith IE. Aminoglutethimide in the treatment of advanced postmenopausal breast cancer. *Cancer Res* 1982, **42** (Suppl.), 3405s–3408s.
3. Cohen MP, Foa PP. Aminoglutethimide inhibition of adrenal desmolase activity. *Proc Soc Exp Biol Med* 1969, **127**, 1086–1090.
4. Santen RJ, Wells SA, Runic S, Gupta C, Kendall J, Ruby EB, Samojlik E. Adrenal suppression with aminoglutethimide. I. Differential effects of aminoglutethimide on glucocorticoid metabolism as a rationale for use of hydrocortisone. *J Clin Endocrinol Metab* 1977, **45**, 469–479.
5. Faglia G, Gattinoni L, Travaglini P, Neri P, Acerbi L, Ambrosi B. Evidence suggesting 11β-hydroxylase inhibition during aminoglutethimide administration. *Metabolism* 1971, **20**, 266–272.
6. Touitou Y, Bogdon A, Legrand JC, Degrez P. Aminoglutethimide and glutethimide: effects on 18-hydroxycorticosterone biosynthesis by human and sheep adrenals in vitro. *Acta Endocrinol Copenh* 1975, **80**, 517–526.
7. Harris AL, Dowsett M, Smith IE, Jeffcoate SL. Endocrine effects of low dose aminoglutethimide alone in advanced postmenopausal breast cancer. *Br J Cancer* 1983, **47**, 621–627.
8. Stuart-Harris R, Dowsett M, D'Souza A, *et al.* Endocrine effects of low dose aminoglutethimide as an aromatase inhibitor in the treatment of breast cancer. *Clin Endocrinol* 1985, **22**, 219–226.
9. Harris AL, Dowsett M, Smith IE, Jeffcoate SL. Hydrocortisone alone versus hydrocortisone plus aminoglutethimide: a comparison of the endocrine effects in postmenopausal breast cancer. *Eur J Cancer Clin Oncol* 1984, **20**, 463–467.
10. Bruning PF, Bonfrer JMG, De Jong-Bakker M, Nooyen W. Influence of ACTH on aminoglutethimide induced reduction of plasma steroids in postmenopausal breast cancer. *J Steroid Biochem* 1984, **21**, 293–298.
11. Santen RJ, Wells SA, Cohn N, Demers LM, Misbin RI, Foltz EL. Compensatory increase in TSH secretion without effect on prolactin secretion in patients treated with aminoglutethimide. *J Clin Endocrinol Metab* 1977, **45**, 739–746.
12. Bruning PF, Bonfrer JGM, Engelsman E, *et al.* Pros and cons of aminoglutethimide for advanced postmenopausal breast cancer. *Breast Cancer Res Treat 1984*, **4**, 289–295.
13. Harris AL, Cantwell BMJ, Carmichael J, *et al.* Phase 2 study of low dose AG: 250 mg/day plus hydrocortisone in advanced postmenopausal breast cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 1105–1111.
14. Harris AL, Dowsett M, Jeffcoate SL, McKinna JA, Morgan M, Smith IE. Endocrine and therapeutic effects of aminoglutethimide in premenopausal patients with breast cancer. *J Clin Endocrinol Metab* 1982, **55**, 718–722.
15. Dowsett M, Harris AL, Smith IE, Jeffcoate SL. Endocrine changes associated with relapse in advanced breast cancer patients on aminoglutethimide therapy. *J Clin Endocrinol Metab* 1984, **58**, 99–104.
16. Harris AL, Dowsett M, Jeffcoate SL, Smith IE. Aminoglutethimide dose and hormone suppression in advanced breast cancer. *Eur J Cancer Clin Oncol* 1983, **19**, 493–498.
17. Dowsett M, Goss PE, Powles TJ, Brodie AMH, Jeffcoate SL. Use of the aromatase inhibitor 4-hydroxyandrostenedione in post menopausal breast cancer: optimization of therapeutic dose and route. *Cancer Res* 1987, **47**, 1957–1961.
18. Stuart-Harris R, Dowsett M, Bozek T, *et al.* Low-dose aminoglutethimide in treatment of advanced breast cancer. *Lancet* 1984, **ii**, 604–607.

19. Coombes RC, Goss P, Dowsett M, Gazet J-C, Brodie AMH. 4-hydroxyandrostenedione in treatment of postmenopausal patients with advanced breast cancer. *Lancet* 1984, ii, 1237–1239.
20. Dowsett M, Lal A, Stein RC, Coombes RC. Dose-related endocrine study of aromatase inhibitor CGS 16949A (abstr.). *J Endocrinol* 1988, **119** (Suppl.).
21. Dowsett M, Harris AL, Stuart-Harris R, *et al.* A comparison of the endocrine effects of low dose aminoglutethimide with and without hydrocortisone in postmenopausal breast cancer patients. *Br J Cancer* 1985, 52, 525–529.
22. Franciosi V, Cocconi G, Bozetti C, Bacchi M. Endocrine effects of low dose aminoglutethimide with (AG) plus hydrocortisone (HC) compared with those of low dose AG alone in postmenopausal advanced breast cancer (abstr.). *Cancer Chemother Pharmacol* 1988, **23** (Suppl.).
23. Rallison ML, Kumagai LF, Tyler FLI. Goitrous hypothyroidism induced by aminoglutethimide, anticonvulsant drug. *J Clin Endocrinol Metab* 1967, 27, 265.
24. Dowsett M, Santner RJ, Santen RJ, Jeffcoate SL, Smith IE. Effective inhibition by low dose aminoglutethimide of peripheral aromatization in postmenopausal breast cancer patients. *Br J Cancer* 1985, 52, 31–34.

Acknowledgements—We would like to thank Ciba-Geigy Pharmaceuticals for financial support of this study.

Eur J Cancer, Vol. 27, No. 7, pp. 849–852, 1991.
Printed in Great Britain

0277–5379/91 $3.00 + 0.00

Tetracosactrin vs. Methylprednisolone in the Prevention of Emesis in Patients Receiving FEC Regimen for Breast Cancer

J. Bonneterre, P. Kerbrat, P. Fargeot, R. Metz, H. Roche, P. Bastit, A. Chevrier, M. Tubiana-Hulin, G. Geyer and P. Cappelaere

0.5 mg tetracosactrin is considered to be equivalent to 40 mg methylprednisolone with regard to the induced cortisol secretion. 97 female breast cancer patients who received their first two FEC courses (epirubicin 50–75 mg/m², 5-fluorouracil 500 mg/m², cyclophosphamide 500 mg/m²) entered this randomised crossover study (76 had previously received an adjuvant treatment); tetracosactrin was administered intramuscularly and methylprednisolone intravenously immediately before chemotherapy administration. The tolerability was evaluated using a diary card during 5 days and patients were asked for their preference at the end of the two cycles. There was no difference either for vomiting (dry heaves were included) or nausea between the two treatments (the analysis was performed on day 1, the worse day of days 2 and 3 and the worse day of days 4 and 5). At day 1, 49% of the patients experienced no or mild nausea after tetracosactrin and 62% after methylprednisolone (not significant) (first period analysis); a complete control of vomiting (including dry heaves) was observed in 49% of the patients after tetracosactrin and 53% after methylprednisolone (not significant). No difference was observed between patients with or without previous chemotherapy. However, slightly more patients preferred tetracosactrin ($P = 0.048$).
Eur J Cancer, Vol. 27, No. 7, pp. 849–852, 1991

INTRODUCTION

EPIRUBICIN, CYCLOPHOSPHAMIDE and 5-fluorouracil are widely used in the treatment of breast cancer either in the advanced stage or as an adjuvant treatment. Most patients experience grade 2 or 3 nausea and vomiting [1]. Glucocorticoids such as dexamethasone or methylprednisolone have been shown to be efficient in the prevention of nausea and vomiting in patients treated with moderately emetogenic chemotherapy agents [2, 3]. Tetracosactrin has been shown to be efficient as a salvage treatment in patients receiving FAC regimen in which doxorubicin was used instead of epirubicin [4]. Although difficult to evaluate, 0.5 mg tetracosactrin induces a cortisol secretion that is thought to be equivalent to 40 mg methylprednisolone [5]. The rationale for this trial was to use a tetracosactrin dose (0.5 mg) which induces a glucocorticoid secretion which is much less than 120 mg methylprednisolone.

PATIENTS AND METHODS

Patients

97 consecutive female breast cancer patients receiving the FEC regimen (epirubicin 50 or 75 mg/m², 5-fluorouracil 500 mg/m², cyclophosphamide 500 mg/m²) entered this trial; both epirubicin doses were accepted since it was a crossover study and since it had been shown that there was no difference in the intensity of nausea and vomiting between the two groups [6]. To be eligible patients should have received their first course with this