Eur J Cancer Clin Oncol, Vol. 20, No. 4, pp. 463–469, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Hydrocortisone alone vs Hydrocortisone plus Aminoglutethimide: a Comparison of the Endocrine Effects in Postmenopausal Breast Cancer

ADRIAN L. HARRIS,*† MITCHELL DOWSETT,‡ IAN E. SMITH* and STEPHEN JEFFCOATE‡

Medical Breast Unit, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, U.K. and ‡Endocrine Department, Chelsea Hospital for Women, Dovehouse Street, London SW3 6LT, U.K.

Abstract—*The endocrine effects of replacement doses of hydrocortisone in postmenopausal women with advanced breast cancer were compared with the same doses of hydrocortisone plus aminoglutethimide. Fifteen patients received aminoglutethimide (AG)* 250 mg *three times a day plus hydrocortisone (HC)* 20 mg *twice a day for* 2 weeks, *then AG was increased to* 250 mg *four times a day. Another* 13 *patients received HC alone for* 2 weeks, *then AG was added. HC alone significantly suppressed oestrone (75% of baseline) and oestradiol (50% of baseline). Addition of AG to these patients produced further oestrone suppression (50% of baseline) significantly greater than HC alone. HC alone suppressed dehydroepiandrosterone sulphate as much as AG + HC. Δ⁴-androstenedione (Δ⁴A) and dehydroepiandrosterone (DHA) were suppressed by HC alone. Addition of AG produced a rise of Δ⁴A to basal levels. These results show that 3-β-ol dehydrogenase is not induced by AG. AG plus HC together from day 1 produced significantly greater oestrone suppression (50% of baseline) than HC alone. Because high-dose steroids may induce aromatase and replacement doses produced marked peripheral endocrine effects, the use of replacement hydrocortisone should be reassessed in advanced breast cancer.*

INTRODUCTION

AMINOGLUTETHIMIDE in combination with hydrocortisone is an effective endocrine therapy in advanced postmenopausal breast cancer [1]. Aminoglutethimide inhibits an early step in adrenal steroid biosynthesis, the conversion of cholesterol to pregnenolone by desmolase [2]. Hydrocortisone in replacement dosage is usually given to prevent a reflex rise in ACTH that may overcome the block [3]. The peripheral conversion of Δ⁴-androstenedione to oestrone by aromatase is the main source of oestrogens in postmenopausal women, and this enzyme system is also inhibited by aminoglutethimide [4, 5].

Earlier reports showed that replacement doses of hydrocortisone alone suppressed urine oestrone in postmenopausal women [6] and that objective tumour responses occurred with replacement doses of corticosterone or hydrocortisone [7–9]. The response rates were lower than reported for aminoglutethimide plus hydrocortisone, but the two therapies have not been compared directly. Aminoglutethimide with hydrocortisone is as effective as adrenalectomy [10], but the only randomised study of adrenalectomy vs replacement hydrocortisone was discontinued when none out of 19 patients responded to the latter treatment [11]. The general consensus is that response to glucocorticoids is infrequent and of short duration [12–15]. The contribution of hydrocortisone to the therapeutic effect of aminoglutethimide is unknown, and the endocrine effects of replacement doses of hydrocortisone in postmenopausal breast cancer are poorly defined. We have therefore compared the endocrine effects of 2 weeks therapy with hydrocortisone followed by the addition of

Accepted 13 September 1983.
†Present address: University Department of Radiotherapy & Clinical Oncology, Newcastle General Hospital, Westgate Road, Newcastle upon Tyne NE4 6BE, U.K.

aminoglutethimide with the effects of starting treatment with aminoglutethimide plus hydrocortisone together.

MATERIALS AND METHODS

All patients had advanced progressing postmenopausal breast cancer. Fifteen patients were started on treatment with aminoglutethimide 250 mg three times a day plus hydrocortisone 20 mg twice a day at 8 a.m. and 8 p.m. for 2 weeks. After 2 weeks the aminoglutethimide dose was increased to 250 mg four times a day.

The next 13 patients were started on treatment with hydrocortisone 20 mg twice a day at 8 a.m. and 8 p.m. for 2 weeks. Aminoglutethimide 250 mg twice a day was then added. The aminoglutethimide dose was then increased by 250 mg at 2-week intervals to the maximum dose of 250 mg four times a day.

Response was assessed by standard UICC criteria [16].

Hormone assays

Blood samples were taken 3 hr after the morning dose of aminoglutethimide and/or hydrocortisone. Samples were taken before treatment, then at 2-week intervals up to 12 weeks from the start of hydrocortisone. Plasma was stored at -20°C until assay. All samples from one patient were measured in one assay. The following hormones were measured by radioimmunoassay using previously described methods [17, 18]: oestrone, oestradiol, dehydroepiandrosterone sulphate (DHAS), Δ^4-androstenedione. Dehydroepiandrosterone (DHA) was measured by radioimmunoassay using the Radioassay Systems Laboratories [^{3}H]-DHA kit. For oestrone, 200 μl of serum is extracted per assay tube and for oestradiol 125 μl per assay tube. Extraction is with purified diethyl ether and buffer blanks are always below the sensitivity limits. Chromatography does not affect the oestrone or oestradiol results.

Results were compared by the paired t test with Bonferoni correction for multiple paired comparisons.

RESULTS

Clinical effects

Hydrocortisone first. There were no side-effects with hydrocortisone in the 13 patients. Aminoglutethimide 250 mg twice a day was then given and one patient developed an influenza-like illness and skin rash, with a progressing pleural effusion. Twelve patients had the aminoglutethimide increased to 250 mg three times a day. Two of these patients were withdrawn at 6 weeks because of progressive disease. Eight of the 10 remaining patients had the dose increased to 250 mg four times a day. The other two remained on 250 mg three times a day for the duration of the study because of side-effects. Side-effects after the addition of aminoglutethimide were similar in type and frequency to those occurring in the patients started with both drugs together (Table 1). In both groups of patients there was a similar response rate to the combination treatment. The clinical features of each group are shown in Table 1.

Endocrine effects

Oestrone suppression. Hydrocortisone alone significantly suppressed oestrone levels at 2 weeks from the start of treatment (Fig. 1). The addition of aminoglutethimide at 2 weeks produced a further signficant suppression of oestrone.

In patients starting treatment with aminoglutethimide plus hydrocortisone, maximal suppression was produced by 2 weeks with no further suppression after that time.

The pretreatment levels of oestrone were higher in the group treated with aminoglutethimide plus hydrocortisone than in those starting on hydrocortisone. The reasons for this do not appear to be related to clinical features (Table 1). The oestrone value as a percentage of the baseline was calculated to make results comparable. The percentage of baseline value at 2 weeks was 75% in the hydrocortisone alone group and 50% in the combination group ($P = 0.0076$). At 4 weeks there was no significant difference. Oestradiol was suppressed by hydrocortisone alone, and a further non-significant fall occurred after addition of aminoglutethimide (pretreatment, 35 ± 6.3 pmol/l; after hydrocortisone 17 ± 3.4 pmol/l; after aminoglutethimide 250 mg twice a day 12 ± 2 pmol/l).

DHAS suppression. There was no difference in pretreatment DHAS levels between the two groups, and at 2 weeks the suppression was the same in the 2 groups (Figs 1, 2). There was a further small significant fall over the next 2 weeks in both groups. Thus hydrocortisone alone suppressed DHAS as much as the combination.

Further endocrine studies in the hydrocortisone first group (Fig. 3)

Oestrone suppression was greater after the addition of aminoglutethimide. However, further dose increments of aminoglutethimide did not produce further oestrone suppression. DHAS levels did not fall further after 1 month, with increasing aminoglutethimide dosage. Δ^4-Androstenedione was significantly suppressed by hydrocortisone at 2 weeks but after addition of aminoglutethimide Δ^4-androstenedione rose

Table 1. Clinical features and aminoglutethimide toxicity in patients given aminoglutethimide plus hydrocortisone or hydrocortisone alone before aminoglutethimide

	Aminoglutethimide plus hydrocortisone	Hydrocortisone first
No.	15	13
Age (yr)		
mean	56.5	58.5
median	57	58
Weight (kg)		
mean	61.1	60.7
median	62	60
Last menstrual period (yr)		
mean	6.5	10.3
median	5	8
Tumor-free interval (months)		
mean	26.2	25.5
median	17	10
Sites of disease		
soft tissue/nodes	11	7
pleura/lung	6	3
bone	11	7
liver	3	2
Previous endocrine therapy	10 (3PR)	4 (2PR)
Previous chemotherapy	3	3
Response to AG + HC	5PR	4PR
Side-effects of AG		
rash	6	4 (+ 1 flu-like illness)
drowsiness	5	3
ataxia	2	-
nausea	2	2
none	8	7

until at 6 weeks from start of treatment there was no longer significant suppression.

DHA was significantly suppressed by hydrocortisone, and remained suppressed on aminoglutethimide. The ratio of Δ^4-androstenedione to DHA was thus increased by the addition of aminoglutethimide (Fig. 4). The rise in Δ^4-androstenedione was not accompanied by an equivalent fall in DHA (Figs 3, 4).

DISCUSSION

This study shows that hydrocortisone alone in a dose of 20 mg twice a day has significant endocrine effects in patients with advanced postmenopausal breast cancer. Oestrone and oestradiol, DHAS, DHA and Δ^4-androstenedione were all suppressed below basal levels. The study was undertaken to try to establish the endocrinological differences between hydrocortisone alone and hydrocortisone plus aminoglutethimide, and therefore explain the reported therapeutic differences of steroids alone compared with aminoglutethimide. There are two differences: oestrone is suppressed more by the combination; Δ^4-androstenedione is not suppressed by the combination.

Although there was a lower pretreatment oestrone in the group starting with hydrocortisone alone, addition of aminoglutethimide resulted in further suppression, and percentage suppression was less than with the combination. This difference in oestrone suppression might account for the relatively lower efficacy of hydrocortisone, since it appears that only about a 50% suppression is required for the therapeutic effect of adrenalectomy or aminoglutethimide plus hydrocortisone. Endogenous oestradiol levels in human breast cancer are 10 times higher than peripheral levels [19]. The contribution of peripheral oestrogens to these concentrations is unknown. However, Δ^4-androstenedione is suppressed by hydrocortisone, and this is an immediate precursor of oestrone production by peripheral aromatase.

There are very few studies of replacement doses of hydrocortisone in advanced breast cancer, but three out of four reports [7–9, 11] did find a reasonable objective response rate of 22–33%

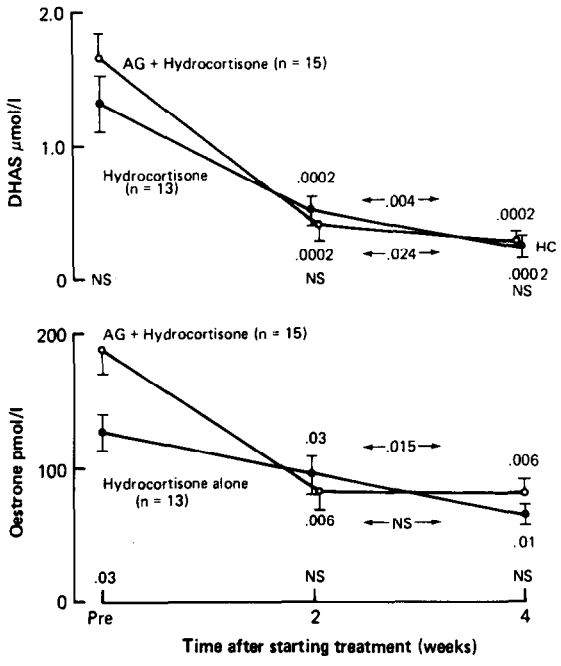

Fig. 1. DHAS and oestrone suppression by hydrocortisone and hydrocortisone plus aminoglutethimide. ●——●, Patients treated initially with hydrocortisone alone and aminoglutethimide added after 2 weeks; ○——○, patients treated initially with aminoglutethimide and hydrocortisone. Significance values are unpaired t tests between the different groups of patients and paired t tests with Bonferoni correction between post- and pretreatment values. The significance value at the bottom of each graph is for the comparison at each time point of patients starting with hydrocortisone alone with those starting on aminoglutethimide plus hydrocortisone. The values above or below each point are for comparison with pretreatment values. The values enclosed by arrows refer to comparison of 2-week with 4-week samples in patients starting hydrocortisone alone (value above lines) or for patients starting aminoglutethimide plus hydrocortisone (value below lines).

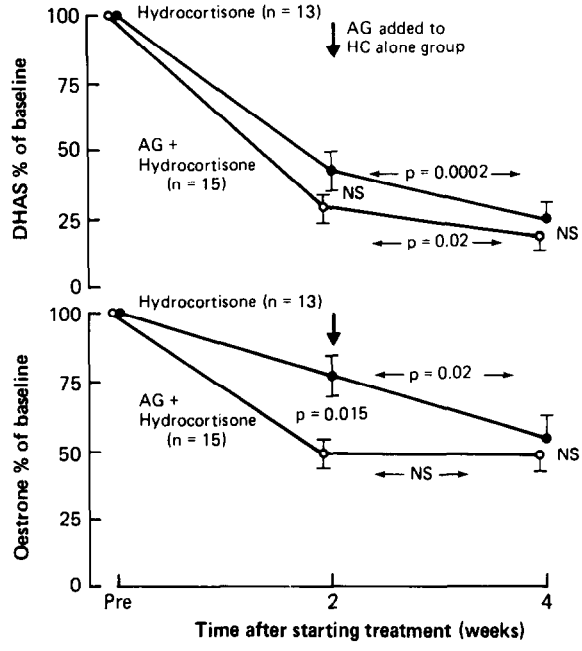

Fig. 2. DHAS and oestrone expressed as percentage of baseline in patients treated with aminoglutethimide plus hydrocortisone, or hydrocortisone alone. ●——●, Patients treated initially with hydrocortisone alone and aminoglutethimide added after 2 weeks; ○——○, patients treated initially with aminoglutethimide and hydrocortisone. Significance values are paired t tests with Bonferoni correction between post- and pretreatment values and between two sets of post-treatment values. The significance value at the bottom of each graph is for the comparison at each time point of patients starting with hydrocortisone alone with those starting on aminoglutethimide plus hydrocortisone. The values above or below each point are for comparison with pretreatment values. The values enclosed by arrows refer to comparison of 2-week with 4-week samples in patients starting with hydrocortisone alone (value above lines) or for patients starting with aminoglutethimide plus hydrocortisone (value below lines).

lasting for a mean of 12 months (range 3–37 months). (In two of the reports, thyroid extract was also given, but this is unlikely to be of physiological relevance.) This contrasts with the short, infrequent responses found with higher-dose steroid therapy [12, 15]. It is possible that endocrine effects of hydrocortisone have been underestimated because of the use of the high doses. It has been shown that high doses of steroids increase human aromatase *in vitro* [20, 21], and they are also immunosuppressive. High-dose glucocorticoids would be expected to virtually eliminate adrenal synthesis of androstenedione, but the significant proportion that is derived from the post-menopausal ovary should be unaffected [22]. If the glucocorticoid also stimulates peripheral aromatization, the overall effect may be to increase oestrogen levels within the tumour. The intermediate degree of suppression produced by low-dose hydrocortisone is associated with responses in between those reported for aminoglutethimide and hydrocortisone and high-dose steroids. There may be a dose-response relationship for hormone suppression and response to endocrine therapy.

The mechanism for the rise in Δ^4-androstenedione on addition of aminoglutethimide is unknown. Santen *et al.* previously suggested that there is increased activity of the enzyme converting DHA to Δ^4-androstenedione (3-β-ol dehydrogenase) [23]. Our study shows that this is unlikely to be the case, since DHA levels did not change significantly, although Δ^4-androstenedione rose markedly. Our previous suggestion that increasing doses of aminoglutethimide block 11-β hydroxylase and cause metabolite accumulation behind the block is more likely [24]. Bird *et al.* [25] have shown there is no increase in conversion of Δ^5 to Δ^4 metabolites in postmenopausal breast cancer patients treated with aminoglutethimide.

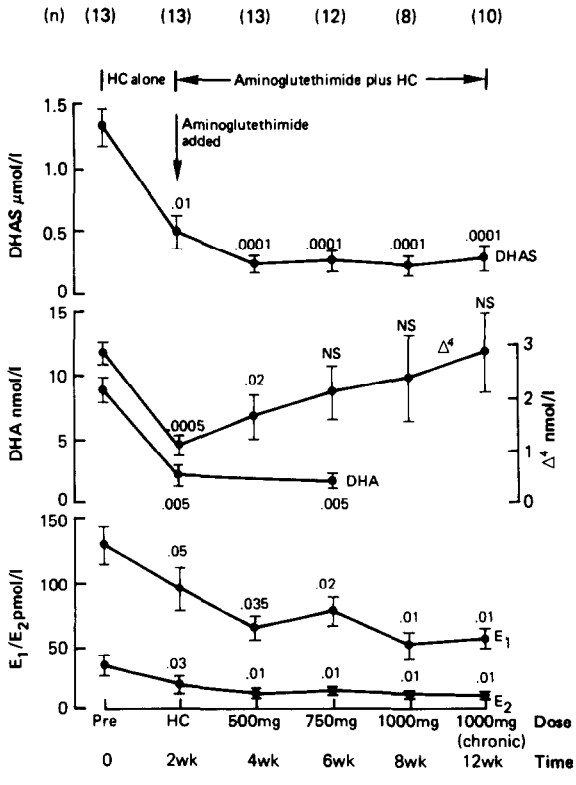

Fig. 3. Serial oestrone, oestradiol, DHAS, DHA and Δ⁴-androstenedione levels in patients starting with hydrocortisone alone. E_1, oestradiol; Δ⁴, Δ⁴-androstenedione. P *values are for paired* t *tests with pretreatment samples, using the Bonferoni correction.*

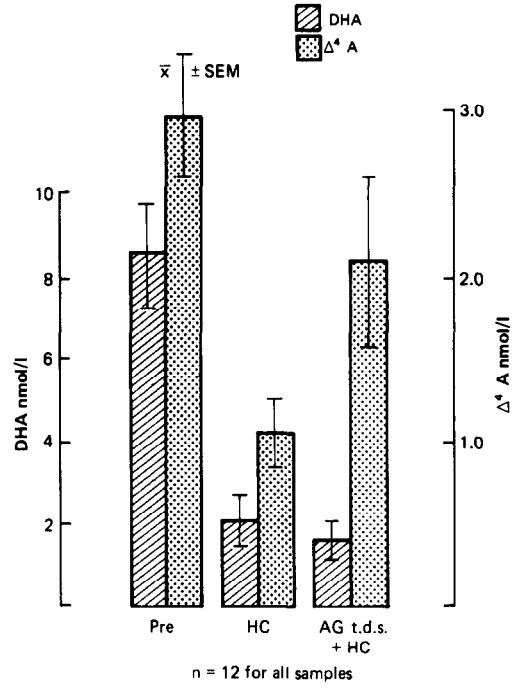

Fig. 4. Comparison of effects of hydrocortisone alone and hydrocortisone plus aminoglutethimide on DHA and Δ⁴-androstenedione (Δ⁴A). Results are for the same patients before hydrocortisone, 2 weeks *after starting hydrocortisone and* 2 weeks *after the addition of aminoglutethimide to the hydrocortisone.*

This study also shows that increasing aminoglutethimide dosage above 250 mg twice a day does not produce further oestrone or oestradiol suppression, a confirmation of our previous study but carried out over a longer time course (2 months) [18].

Increasing the aminoglutethimide dosage slowly did not reduce the severity of side-effects compared to increasing the dosage over 1 month. This may be because aminoglutethimide induces its own metabolism within a week of the start of therapy and therefore more prolonged dose build-up does not affect the plasma levels [26].

Borkowski *et al.* examined the effects of 3 mg/day dexamethasone in six patients with advanced postmenopausal breast cancer (dose equivalent to 100 mg cortisone/day) [27]. They found oestrone and oestradiol suppression were slower in onset than in normal women, and suggested that peripheral aromatization of adrenal precursors within the tumour may be a site of oestrogen production. Paridaens *et al.* [28] found in four patients that oestradiol was not suppressed with 40 mg hydrocortisone, in contrast to our study.

It is possible that had the hydrocortisone been continued longer, further oestrogen suppression may have occurred. Borkowski *et al.* [27] found that suppression took several weeks. The present study cannot assess this, but because of the marked hormone effects of hydrocortisone, investigation of the endocrine effects of longer courses may be worthwhile.

The present studies show that hydrocortisone 20 mg twice a day has marked effects on the peripheral endocrine environment and suggests that, in view of its excellent tolerance, it should be reassessed in advanced breast cancer. Higher doses may have adverse effects and no greater oestrone suppression. Aminoglutethimide in combination with hydrocortisone produces a greater and more rapid fall in oestrone than hydrocortisone alone. We have previously shown that aminoglutethimide alone produced equivalent oestrone suppression to aminoglutethimide plus hydrocortisone [24], and so it is unlikely that hydrocortisone contributes to the therapeutic effect of aminoglutethimide via oestrone suppression. However, the role of hydrocortisone in preventing the rise in Δ⁴-androstenedione produced by aminoglutethimide alone may be important in depriving peripheral tissues of a substrate for aromatase.

REFERENCES

1. HARRIS AL, POWLES TJ, SMITH IE. Aminoglutethimide in the treatment of advanced postmenopausal breast cancer. *Cancer Res* 1982, **42**, 3405S–3408S.
2. CASH R, BROUGH AJ, COHEN MNP, SATOH PS. Aminoglutethimide as an inhibitor of adrenal steroidogenesis: mechanism of action and therapeutic trial. *J Clin Endocrinol Metab* 1967, **27**, 1239–1248.
3. SANTEN RJ, LIPTON A, KENDALL J. Successful medical adrenalectomy with aminoglutethimide. Role of altered drug metabolism. *JAMA* 1974, **230**, 1661–1665.
4. GORDIN JM, SIITERI PK, MACDONALD PC. Source of estrogen production in postmenopausal women. *J Clin Endocrinol Metab* 1973, **36**, 207–212.
5. 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.
6. NISSENMEYER R, SANNER T. The excretion of oestrone, pregnanediol and pregnanetriol in breast cancer patients. *Acta Endocrinol* 1963, **44**, 334–345.
7. BETHUNE GW. Cortisone in palliative treatment of breast cancer. *Can J Surg* 1964, **7**, 289–292.
8. GORDAN GS, GRAHAM WP III, GOLDMAN L *et al.* Hormonal treatment of disseminated cancer of the female breast. *Calif Med* 1963, **98**, 189–194.
9. LEMON HM. Cortisone-thyroid therapy of metastatic mammary cancer. *Ann Intern Med* 1957, **46**, 457–484.
10. SANTEN RJ, WORGUL TJ, SAMOJLIK E *et al.* A randomised trial comparing surgical adrenalectomy with aminoglutethimide plus hydrocortisone in women with advanced breast cancer. *N Engl J Med* 1981, **305**, 545–551.
11. DAO TL, TAN E, BROOKS V. A comparative evaluation of adrenalectomy and cortisone in the treatment of advanced mammary carcinoma. *Cancer* 1961, **14**, 1259–1265.
12. PEARSON OH, LI MC, MACLEAN JP, LIPSETT MB, WEST CD. The use of hydrocortisone in cancer. *Ann NY Acad Sci* 1955, **61**, 393–396.
13. STOLL BA. Dexamethasone in advanced breast cancer. *Cancer* 1960, **13**, 1074–1080.
14. KOFMAN S, NAGAMANI D, BUERGER RE, TAYLOR SG III. The use of prednisolone in the treatment of disseminated breast cancer. *Cancer* 1958, **11**, 226–232.
15. GEIMER NF, DONEGAN WL. Role and mechanism of corticosteroid therapy. In: STOLL BA, ed. *Systemic Control of Breast Cancer*. London, Weinneman, 1981, 297–325.
16. HAYWARD JL, CARBONE PP, HEUSON J-C, KUMAOKA S, SEGALOFF A, RUBENS RD. Assessment of response to therapy in advanced cancer. *Eur J Cancer* 1977, **13**, 89–94.
17. 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.
18. 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.
19. EDERY M, GOUSSARD J, REHENNIN L, SCHOLLER R, REIFFSTECK J, DRODOWSKY MA. Endogenous oestradiol 17β concentrations in breast tumours determined by mass fragmentography and by radioimmunoassay: relationship to receptor content. *Eur J Cancer* 1981, **17**, 115–120.
20. MENDELSON CR, CLELAND WH, SMITH ME, SIMPSON ER. Regulation of aromatase activity of stromal cells derived from human adipose tissue. *Endocrinology* 1982, **111**, 1077–1085.
21. SIMPSON ER, ACKERMAN GE, SMITH ME, MENDELSON CR. Estrogen formation in stromal cells of adipose tissue of women: induction by glucocorticoids. *Proc Natl Acad Sci USA* 1981, **78**, 5690–5694.
22. VERMEULEN A. The hormonal activity of the postmenopausal ovary. *J Clin Endocrinol Metab* 1976, **42**, 247–253.
23. SAMOJLIK E, SANTEN RJ. Adrenal suppression with aminoglutethimide. III. Comparison of plasma Δ^4 and Δ^5-steroids in postmenopausal women treated for breast carcinoma. *J Clin Endocrinol Metab* 1978, **47**, 717–724.
24. 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.
25. BIRD CE, MASTERS VE, STERNS EE, CLARK AF. Effects of aminoglutethimide on Δ^5-androstenediol metabolism in postmenopausal women with breast cancer. *Cancer Res* 1982, **42**, 4797–4800.

26. MURRAY FT, SANTNER S, SAMOJLIK E, SANTEN RJ. Serum aminoglutethimide levels: studies of serum half-life, clearance and patient compliance. *J Clin Pharmacol* 1979, **19**, 704–711.
27. BORKOWSKI A, L'HERMITE M, DOR P *et al.* Steroid sex hormones and prolactin in postmenopausal women with generalised mammary carcinoma during prolonged dexamethasone treatment. *J Endocrinol* 1977, **73**, 235–246.
28. PARIDAENS R, VERMEULEN A, HEUSON JC. The inhibiting influence of increasing doses of aminoglutethimide on adrenal function and oestrogen production. In: PAESI FJA, ed. *Aminoglutethimide*. Switzerland, Ciba-Geigy, 1982, 72–76.