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Endocrine Effects of Aminoglutethimide Plus Hydrocortisone Versus Effects of High Dose of Hydrocortisone Alone in Postmenopausal Metastatic Breast Cancer

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Abstract—*Aminoglutethimide (Ag) has been used in different dosages with and without combined treatment with glucocorticoids for the suppression of peripheral plasma levels of steroidal hormones. In the present work we have estimated changes in peripheral steroid levels after 3 days of adrenal suppression with a 'physiological' daily dose of* 40 mg *hydrocortisone (H). Subsequently Ag* (1000 mg *daily) was added or the dose of H was doubled in order to study the efficacy of the suppression of oestradiol by these conditions during a 6-week period. Sixteen postmenopausal patients with evaluable and measurable progressive breast cancer were selected for the initial treatment, thereafter Ag was added in eight patients, while the other eight patients continued on H with a double dose.*

Administration of 40 mg *H daily during the first 3 days caused a significant decrease of plasma oestradiol* ($P < 0.01$), *androstenedione* ($P < 0.01$) *and DHEA-S* ($P < 0.05$). *Basal plasma cortisol levels increased and the diurnal rhythm disappeared. These observations suggest suppression of adrenal function by the exogenous cortisol. Prolonged treatment with a higher dose of H* (80 mg *daily) caused further suppression of androstenedione* ($P < 0.01$) *but not of oestradiol. The addition of* 1000 mg *of Ag to H had no further significant effect on plasma oestradiol levels either. The main difference between the effects of the two treatment modalities was in the levels of androgens. The group treated with H alone showed long-term significant suppression of both androstenedione and DHEA-S, while in the group treated with the combination of H + Ag a further pronounced suppression of DHEA-S and elevation of androstenedione was found. Finally, there was a significant difference between SHBG levels in the two groups at day* 42. *The increased levels of SHBG in the H + Ag-treated group might lower the 'free' oestradiol concentration. It is concluded that both drugs have different effects on the plasma levels of peripheral steroids. On theoretical grounds, the combination of H + Ag might be preferable, because 'free' oestradiol plasma levels may be lowest after this treatment. However, a direct correlation with clinical effects still remains to be proven.*

INTRODUCTION

OESTROGENS play the most important role in maintaining the growth of established breast cancer [1]. Therefore, suppression of circulating plasma levels of oestrogens may induce regression of tumour growth. In premenopausal women the ovaries are the main source of oestrogens, but in postmenopausal women oestrogens are mainly derived from extra-ovarian aromatization of androgenic precursors such as androstenedione [2, 3].

Aminoglutethimide has been shown to be highly effective as an aromatase inhibitor, but it also inhibits several adrenal enzymes involved in steroid biosynthesis, i.e. desmolase, 3β-hydroxysteroid-dehydrogenase, 21-hydroxylase, 18-hydroxylase and 11β-hydroxylase [4, 5]. During single treatment with aminoglutethimide the inhibition of 11β-hydroxylase and 21-hydroxylase causes a marked rise of peripheral concentrations of 17-hydroxy progesterone and androstenedione which steroid is a substrate for the aromatase which converts androgens to oestrogens [4–11]. Inhibition of adrenal

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enzymes may lead to decreased cortisol and aldosterone secretion. However, the inhibition of desmolase and the other enzymes can be easily overridden by the action of exogenous [6] or endogenous [12–14] ACTH. This indicates that in order to inhibit adrenal function with aminoglutethimide, dexamethasone [12, 13] or preferentially hydrocortisone [14] must be additionally given to prevent a reflex rise in ACTH, which may overcome the blocks in adrenal steroid biosynthesis.

Aminoglutethimide has been used in different dosages with or without additional administration of hydrocortisone [4–22]. Single treatment with both hydrocortisone or aminoglutethimide can suppress plasma oestrogen concentrations. In recent years most investigators have studied effects of combination treatment with hydrocortisone in comparison with (low dose) aminoglutethimide alone, while only a few of them studied the effects of combination treatment in comparison with single treatment with hydrocortisone. Two reports in which treatment with aminoglutethimide plus hydrocortisone (with respect to endocrine effects) was compared with short-term treatment with hydrocortisone alone showed a significant additional suppression of plasma concentrations of oestrone when aminoglutethimide was added [7, 20, 21]. On the other hand, the suppression of plasma levels of oestradiol, the biologically most active oestrogen, was not significantly different between both treatment modalities. In contrast Vermeulen reported recently that suppressed plasma oestradiol concentrations increased significantly to pretreatment values within 2 weeks, when aminoglutethimide administration was stopped during combination treatment but treatment with 40 mg hydrocortisone was continued [9].

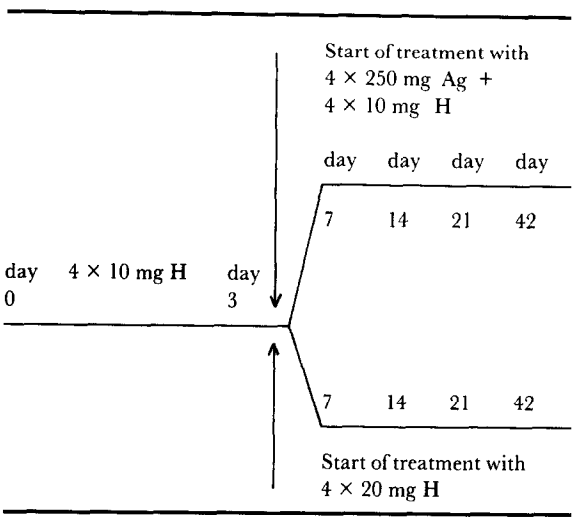
In the present paper we studied the changes in peripheral steroid hormone levels after administration of a 'physiological' dose of hydrocortisone (40 mg daily). Subsequently we have compared in the same patient group the endocrine effects of long-term treatment with a pharmacological dose of hydrocortisone (80 mg per day) with those observed during treatment with 4 × 250 mg aminoglutethimide in combination with the usual dose of 40 mg hydrocortisone. In addition, we have looked for changes in plasma concentrations of sex hormone binding globulin (SHBG), a factor which was not studied before during aminoglutethimide treatment.

MATERIALS AND METHODS

Patients

Sixteen patients with evaluable and measurable progressive metastatic breast cancer were selected for this study after informed consent to participate in this study was obtained. All patients except one (previous ovariectomy) were in natural menopause (> 2 years since last menstruation) and between 47 and 74 years of age. They had been heavily pretreated for metastatic breast cancer but their life-expectancy was longer than 3 months.

Table 1. Treatment modalities



H = Hydrocortisone, Ag = aminoglutethimide.

Treatment modalities

The patients received the following treatment during a total period of 6 weeks (Table 1). All patients received 40 mg hydrocortisone daily (4 × 10 mg) during 3 days; thereafter patients were randomized in two groups of eight patients. Patients in the first group were treated with 1000 mg aminoglutethimide (4 × 250 mg daily) in combination with the same dose of 40 mg hydrocortisone, while patients in the second group were treated with a pharmacological dose of 80 mg of hydrocortisone (4 × 20 mg daily). The treatment was continued until tumour progression but the endpoint of this endocrine study was at 42 days of treatment. Both at the start and the end of the study routine clinical and biochemical investigations were performed. In addition, on days 0 and 42 blood was collected at 8.00 h for estimation of plasma concentrations of oestradiol, androstenedione, dehydroepiandrosterone sulphate (DHEA-S), SHBG, the gonadotropins LH and FSH, prolactin (PRL), growth hormone (GH), thyroid function (TSH, T3, T4), cortisol, desoxycortisol (compound-S), 17-hydroxyprogesterone, glucose and insulin. Some of these compounds were also measured at the same time of the day at more frequent intervals, i.e. on days 0, 3, 7, 14, 21 and 42, while on days 0 and 7 additional blood samples for estimation of cortisol were collected (Table 3). Fourteen fully evaluable patients completed the study which allowed analysis with respect to the endocrine effects.

Laboratory investigations

Plasma cortisol concentrations were estimated by radio-immunoassay, using kits provided by Clinical Assays (Cambridge, MA). Inter- and intra-assay variations were 9.5 and 8.0%, respectively. Concentrations of DHEA-S and androstenedione were estimated using radioimmunoassay kits provided by EIR (Würenlingen, Switzerland). Inter- and intra-assay variations were 10.7 and 8.6% for DHEA-S and 17.3 and 7.9% for androstenedione. 17-Hydroxy progesterone was estimated by radioimunoassay, using antibodies raised in the Department of Biochemistry, Division of Chemical Endocrinology, Erasmus University, Rotterdam. Inter- and intra-assay variations were 12.3 and 7.0%. Methods used for the estimations of plasma levels of eostradiol, SHBG, gonadotropins, prolactin, GH, TSH, T3, T4, compound-S, glucose and insulin have been reported previously [23].

Statistics

Paired *t*-tests were used to determine the statistical significance of the difference between values observed during treatment in comparison to pretreatment values while unpaired *t*-tests were used to compare the plasma hormone levels found in the two treatment groups.

RESULTS

A. *Endocrine effects*

1. *Oestradiol.* Hydrocortisone alone produced a significant fall in mean plasma oestradiol levels from 29.1 to 21.8 pmol/l ($P < 0.01$) at day 3 of treatment (Table 2). After randomization addition of aminoglutethimide or doubling the dose of hydrocortisone caused no significant further decrease in the plasma concentrations of this hormone (Table 3), although the total decrease compared to pretreatment concentrations was greater in the group of patients treated with aminoglutethimide plus hydrocortisone (41%) than in the group of patients treated with hydrocortisone alone (12%).

2. *Androstenedione.* A significant decrease of the mean plasma concentration of androstenedione from 2.56 to 1.09 nmol/l ($P < 0.01$) was found after 3 days of treatment with a daily dose of 40 mg hydrocortisone alone (Table 2). In the group treated with 80 mg of hydrocortisone this decrease became more evident with time (Table 3) and levels of androstenedione at 21 and 42 days of treatment were significantly lower than after 3 days of treatment with 40 mg hydrocortisone ($P < 0.01$ and $P < 0.05$, respectively). In the group treated with the combination of hydrocortisone and aminoglutethimide mean androstenedione concentrations increased at days 14 and 21 of treatment compared to levels at days 3 and 7 (Table 2 and 3). These values were not significantly different from those found before treatment (Table 3).

3. *DHEA-S.* Hydrocortisone alone (40 mg daily) produced after 3 days a significant decrease of mean plasma concentrations of DHEA-S from 0.34 to 0.17 nmol/l ($P < 0.05$) (Table 2). A further decrease was obtained after administration of the double dose of hydrocortisone (80 mg daily) ($P < 0.05$) (Table 3). This mean level remained unchanged at 0.09 nmol/l during the rest of the treatment period. With the addition of aminoglutethimide to 40 mg hydrocortisone DHEA-S levels were suppressed to significantly lower values than those found in the group of patients treated with 80 mg hydrocortisone alone (Table 3).

4. *Cortisol.* After the start of treatment with 40 mg hydrocortisone a significant increase of mean plasma cortisol levels was found both at 8.00 and 16.00 h on day 3 (Table 2). At 8.00 h we did not observe a significant increase in the two sub-groups after randomization (Table 3). Only on day 7 was there a significant increase in the group treated with aminoglutethimide and 40 mg hydrocortisone as compared to pretreatment. Plasma cortisol concentrations at 16.00 h were measured only during the first phase of the study. At day 7, the group treated with the high dose of hydrocortisone showed a significant higher mean plasma cortisol level in comparison to mean concentrations in patients who received the combination of aminoglutethimide and hydrocortisone (Table 3). The diurnal rhythm of cortisol levels, which was present before the start of treatment, was no longer maintained during therapy in both groups of patients.

5. *SHBG.* The combination treatment with aminoglutethimide and hydrocortisone caused a significant increase ($P < 0.01$) of plasma levels of SHBG in comparison to pretreatment values (Table 3). After 42 days of treatment SHBG levels were significantly ($P < 0.05$) higher in patients receiving the combination treatment than in patients receiving a high dose of hydrocortisone alone.

6. *T4, T3, TSH.* Both treatment regimens caused a slight decrease of both T4 and T3, and a slight increase of TSH at the end of the treatment period. This increase was significant ($P < 0.05$) in the group treated with aminoglutethimide plus hydrocortisone after 6 weeks of treatment (data not shown).

Table 2. Effect of hydrocortisone administration on endocrine parameters in postmenopausal patients with metastatic breast cancer (results are given as mean ± S.D., n = 16)

Parameter	Before treatment	After 3 days of 40 mg hydrocortisone daily
1. Oestradiol (pmol/l)	29.1 ± 14.3	21.8 ± 6.9**
2. Androstenedione (nmol/l)	2.56 ± 1.95	1.09 ± 0.69**
3. DHEA-S (mmol/l)	0.34 ± 0.35	0.17 ± 0.19*
4. Cortisol 8.00 h (nmol/l)	501 ± 145	625 ± 183*
5. Cortisol 16.00 h (nmol)l)	345 ± 169	534 ± 199**

*$P < 0.05$; **$P < 0.01$, compared with hormone levels before treatment (paired Student's *t*-test).

7. *Glucose and insulin.* We did not observe significant changes in plasma glucose and insulin concentrations after 6 weeks of both types of treatment (data not shown).

8. *Gonadotropins, prolactin, growth hormone, deoxycortisol and 17-hydroxy progesterone.* There were no significant changes of the mean levels of these hormones during treatment (data not shown). It should be mentioned, however, that in one patient on hydrocortisone plus aminoglutethimide therapy an exceptional increase of 17-hydroxy progesterone, deoxycortisol and androstenedione was found at day 42. This patient also developed skin exanthema. Drug hypersensitivity or slow metabolism of aminoglutethimide resulting in a higher plasma concentration and aminoglutethimide in this single patient might be possible explanations for these phenomena. Therefore, results in this patient were excluded from the final analysis at day 42.

B. *Clinical effects*

Clinical results were rather poor as could be expected for these patients with very advanced breast cancer: partial remission in one patient, stable disease in five patients, while the other 10 patients remained progressive. Since investigation of clinical effects was not the main object of this study these are not further discussed. It should be mentioned that temporary toxic exanthema appeared in four patients treated with aminoglutethimide, but interruption of therapy was not necessary. The drug was tolerated well, without side-effects on the central nervous system.

DISCUSSION

During the first 3 days of the study the effect of 40 mg hydrocortisone administered daily was investigated (Table 2). A significant decrease in the plasma concentrations of oestradiol, androstenedione and DHEA-S was found. Basal plasma cortisol increased and the diurnal rhythm disappeared. This observation indicates suppression of pituitary–adrenal function by the exogenous dose of hydrocortisone used. Prolonged daily treatment with a higher dose of 80 mg hydrocortisone (Table 3) caused further suppression of both DHEA-S and androstenedione while oestradiol levels remained unchanged. The high dose of glucocorticoids was expected to suppress adrenal hormone synthesis and secretion of androstenedione and DHEA-S. As these compounds are precursors of oestrogens, this might be of benefit in the treatment of breast cancer. On the other hand, it has been reported that aromatase activity of human adipose stromal cells in tissue culture is stimulated by glucocorticoids [24, 25], which might result in an opposite effect.

The addition of aminoglutethimide (1000 mg) to hydrocortisone had no significant further suppressive effects on plasma oestradiol levels (Table 3). Although the oestradiol concentrations tended to be more lowered in the group of patients treated with the combination of aminoglutethimide plus hydrocortisone we found a similar suppression of oestradiol with subsequent slight (not significant) rise of gonadotropins with both treatment modalities. This is in agreement with results of the studies of Paridaens [20, 21] and of Harris [7], who observed also a further non-significant fall of oestradiol after addition of aminoglutethimide to hydro-

Table 3. *Effects of hydrocortisone* 80 mg (*H*) *or combination aminoglutethimide* 1000 mg *and hydrocortisone* 40 mg (*H* + *AG*) *on endocrine parameters in postmenopausal metastatic breast cancer patients* (*results are given as means* ± S.D., *n* = 6–8)

Parameter	Before treatment		During treatment							
	Day 0		Day 7		Day 14		Day 21		Day 42	
	H	H + Ag	H	H + Ag	H	H + Ag	H	H + Ag	H	H + Ag
1. Oestradiol (pmol/l)	27.4 ± 14.5	30.9 ± 14.8	22.2 ± 7.0	20.0 ± 9.1	22.9 ± 6.8	23.9 ± 8.3	22.5 ± 6.3	26.2 ± 6.3	24.1 ± 11.9	18.3 ± 9.1
2. Androstenedione (nmol/l)	3.08 ± 2.46	2.04 ± 1.20	1.07 ± 0.90†	0.98 ± 0.90	0.92 ± 0.53†	2.64 ± 2.63	0.43 ± 0.30†	2.11 ± 2.37	0.58 ± 0.46†	1.01 ± 0.56
3. DHEA-S (nmol/l)	0.41 ± 0.38	0.27 ± 0.32	0.09 ± 0.08†	0.02 ± 0.03*	0.09 ± 0.08†	0.03 ± 0.04	0.09 ± 0.07†	0.01 ± 0.0**	0.09 ± 0.09†	0.01 ± 0.0*
4. Cortisol 8.00 h (nmol/l)	549 ± 155	454 ± 125	660 ± 357	734 ± 137††	514 ± 394	628 ± 237	649 ± 374	632 ± 290	691 ± 290	424 ± 306
5. Cortisol 16.00 h (nmol/l)	433 ± 184	256 ± 98*	865 ± 156††	616 ± 242††*						
6. SHBG (nmol/l)	88.5 ± 59.4	65.0 ± 14.5							66.0 ± 27.3	98.3 ± 20.8††*

†$P < 0.05$ vs. day 0; ††$P < 0.01$ vs. day 0; *$P < 0.05$ between 2 treatment modalities; **$P < 0.01$ between 2 treatment modalities.

cortisone. Furthermore, Stuart-Harris *et al.* [15, 16] found a maximal suppression of oestradiol levels at the lowest dose of aminoglutethimide which they used (2 × 62.5 mg daily); higher doses of aminoglutethimide or combination with hydrocortisone failed to cause further suppression. However, in a later study [10] they reported that, when plasma oestradiol levels were expressed as a percentage of pretreatment values, the combination treatment caused a significantly ($P = 0.04$) more pronounced suppression compared to treatment with aminoglutethimide alone.

The main difference between the two treatment groups in our study was in the circulating androgen levels. The group treated with hydrocortisone alone showed a significant further suppression of both DHEA-S and androstenedione during long-term therapy, while in the group treated with the combination of hydrocortisone plus aminoglutethimide only a further pronounced suppression of DHEA-S was found in the presence of an elevation of androstenedione levels (Table 3) compared with the results in patients treated with hydrocortisone alone. These results are in agreement with those of several authors demonstrating that treatment with aminoglutethimide increased plasma concentrations of androstendione, while plasma DHEA-S levels remained unchanged or decreased slightly [4, 6–11, 22]. This increase of androstenedione could be explained by a block in the enzymes which convert progesterone and 17-hydroxy progesterone to the 21- and 11β-hydroxylated steroids [4, 6]. The increase of 17-hydroxy progesterone [4, 6, 8, 9, 11] and desoxycortisol [8, 9] observed during single treatment with aminoglutethimide could not be observed in our study concerning combination treatment with hydrocortisone. Harris also found no increase of 17-hydroxy progesterone during combination treatment with hydrocortisone [6].

In our study there was a significant difference between SHBG levels in the two groups of patients at day 42 (Table 3). The reason for this difference is not clear, especially not since androgens can have a suppressive effect on SHBG concentrations [26]. The circulating concentration of androstenedione, the precursor for peripheral conversion to testosterone, is higher in the patients treated with the combination of aminoglutethimide and hydrocortisone than in the patients who received only hydrocortisone. Mean plasma concentrations of testosterone have been reported to remain constant [9, 21] or to be suppressed [27] during combination therapy. The increased levels of SHBG might lower the 'free' oestradiol concentration in the group treated with the combination of the two drugs.

The suppressive effect of aminoglutethimide on thyroid function was described previously by Santen *et al.* [28]. Prolactin levels remained unchanged despite the lowering of oestradiol levels ([28], this study).

The question remains whether the combination of both drugs using the conventional dose regimen (1000 mg aminoglutethimide + 40 mg hydrocortisone) is optimal. The use of lower doses of aminoglutethimide, which cause the same endocrine effects, might be more rational as suggested by Harris [6], and confirmed recently by Bonneterre *et al.* [17] who used 500 mg of aminoglutethimide in combination with 40 mg hydrocortisone daily. However, lower doses of aminoglutethimide (2 × 125 mg daily) without hydrocortisone replacement showed less reduction of aromatase activity compared to 1000 mg [8], less pronounced suppression of plasma oestradiol levels [10], lower clinical response compared with combination treatment with hydrocortisone and the potential risk of the development of adrenal insufficiency [18, 19]. On the other hand, Hoffken *et al.* [22] did not observe adrenal insufficiency in 38 patients treated with a dose of even 4 × 250 mg aminoglutethimide without hydrocortisone supplementation during up to 15 months, but the objective response rate was relatively low. In addition, it has to be noted that as reported for hydrocortisone [29] aminoglutethimide may have direct effects on human breast tumours [30, 31] which appear to contain significant aromatase activity in 79 out of 128 (62%) tumours [31].

Our study demonstrated that hydrocortisone alone exerted marked effects on the peripheral endocrine environment, which may cause tumour regression. In a recent study treatment with prednisone appeared as effective as the common treatment with medroxyprogesterone acetate [32]. In addition, substantial clinical improvement has been reported on corticoids alone also in earlier studies [33–35]. Since modern criteria for assessment of response were not used, a reassessment of clinical response to corticosteroid monotherapy compared with effects of the above-mentioned combination of aminoglutethimide and hydrocortisone would be of value. It is not possible to draw conclusions on this point from the results of the present relatively short-term, biochemically directed study.

In conclusion, the endocrine effects of administration of the combination aminoglutethimide and hydrocortisone differ from those of hydrocortisone alone. Because of the large suppression of 'free' oestradiol levels, the combination may be superior to the effect of the single drugs in the treatment of metastatic breast cancer. However, a direct correlation with clinical benefit has not been demonstrated yet.

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