Adrenal Steroid Levels in Castrated Men with Prostatic Carcinoma Treated with Aminoglutethimide plus Hydrocortisone

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ABSTRACT

Monthly serum dehydroepiandrosterone sulfate, androstenedione, testosterone, dehydroepiandrosterone, and free testosterone levels were measured in 94 of 129 patients with castration resistant prostatic carcinoma treated on a clinical protocol with aminoglutethimide (1000 mg/day) plus hydrocortisone (40 mg/day). Base-line steroid levels were not found to be age related. Therapy reduced the median levels of all monitored steroids but this suppression was not uniform. Although 87% of dehydroepiandrosterone sulfate levels were suppressed compared to base-line measurements, only 52% of androstenedione and 49% of testosterone levels were reduced. Androstenedione levels in 34% of patients actually rose to greater than twice base-line levels with similar but less frequent rises seen in testosterone, free testosterone, and dehydrotestosterone levels. The highest testosterone level measured was 190 ng/ml. Neither the cause, the deviation, nor the clinical significance of the androgen rise seen in these patients was established. Therapy with aminoglutethimide plus hydrocortisone as administered in this study may not uniformly achieve the objective of suppressing adrenal androgen production.

INTRODUCTION

The suppression or elimination of testicular androgen production is the only proven effective systemic therapy for metastatic prostatic carcinoma (1). Endocrine induced remissions persist for an average of less than 2 years and median survival from the date of subsequent relapse is only 6 months (2). Adrenal steroid production is also a source of androgen production and is not affected by most primary therapies directed toward the testes (3). Consequently, adrenal suppression has become a proposed method of second line hormonal therapy in prostate cancer (4).

Although surgical adrenalectomy in patients with prostatic carcinoma progressing after castration leads to a more complete reduction in serum androgen levels (5), the significant morbidity and mortality risk of this major surgical procedure has precluded its routine application (6). Aminoglutethimide (AGT) is an aromatase inhibitor and a potent inhibitor of adrenal corticosteroid synthesis (7). Although all the effects of aminoglutethimide on the complex metabolic pathways in the adrenals have not been delineated, a major site of action is in the cortex where the conversion of cholesterol to pregnenolone is inhibited (8).

Studies conducted primarily in women with breast carcinoma have demonstrated that this drug can suppress some adrenal steroid levels (9). However, uncertainty exists over whether aminoglutethimide can significantly inhibit the production of androgenic steroids by the adrenal cortex (10, 11). We report herein the results of serial serum adrenal steroid measurements in 94 of 129 castrated men with metastatic prostatic carcinoma treated with aminoglutethimide plus hydrocortisone.

MATERIALS AND METHODS

Study Group and Clinical Trial Design. The Aminoglutethimide Study Group (Appendix A) is composed of 15 institutions who instituted a Phase II clinical trial in 1983 to determine whether therapy with AGT plus HC had significant clinical activity in previously castrated men with progressive, evaluable, or measurable, prostatic carcinoma. Additional eligibility criteria included normal hematopoietic, renal, and hepatic function, histologically documented prostatic carcinoma, informed written consent, and a life expectancy in excess of 3 months. Therapy consisted of AGT at a dose of 250 mg p.o. twice a day for 2 weeks with the dose then escalated to 250 mg four times a day. Hydrocortisone was concurrently administered p.o. at an initial total daily dose of 100 mg with the dose then reduced to a maintenance dose of 40 mg/day after 2 weeks of therapy. All patients were initially treated for 3 months unless frank disease progression occurred. At the end of 3 months, measurable or evaluable disease parameters were reassessed and a response determination was made by using National Prostate Cancer Project criteria (12). Patients who achieved disease regression (partial or complete) or disease stabilization were continued on AGT plus HC therapy until disease progression was documented. Patients with disease progression had their therapy discontinued and were removed from study.

Adrenal Steroid Levels. Serum samples were collected on all patients prior to initiation of therapy and 4, 8, and 12 weeks later with the study design calling for the blood sampling to be performed at approximately the same time each morning. Serum was stored frozen at -20°C. Assays for levels of DHEA-S, AND, testosterone, DHT, and FT were carried out at Nichols Institute Laboratories in San Juan Capistrano, CA.

DHEA-S levels were quantified by a direct RIA with the lower limit of sensitivity being 5 /¿g/dl. Separate RIAs were also used to measure levels of AND, DHT, and testosterone levels. The lower limits of sensitivity for these assays were 6 ng/dl for AND, 3 ng/dl for DHT, and 1 ng/dl for testosterone. FT was quantified after equilibrium dialysis with a lower limit of sensitivity of 1.2 pg/ml.

Statistical Methodology. Timed steroid levels for the entire population and subpopulations were recorded as means and medians. A two-sided Wilcoxon signed rank test adjusted for ties and zeroes was applied to determine the significance of change in median steroid levels over time (13). A relationship between clinical variables and steroid levels was assessed by linear regression analyses (14). A x2 table was used to determine the significance of relationships between therapy response rates and rising or falling adrenal steroid levels (15).

RESULTS

Clinical Results. Detailed results from the clinical trial are reported elsewhere (1). In brief, 129 patients were enrolled and 86 (67%) were evaluable for response. Using National Prostate Cancer Project response criteria, partial tumor regressions were seen in 11 patients (13%). Stable disease criteria were documented in 41 patients (48%), and frank disease progression was seen in 2 patients (2%).
documented in 34 patients (39%). Overall mean survival for the entire study group was 13.3 ± 9.3 (SD) months. Mean survival for partial responders was 20.1 ± 8.1 months in comparison to 17.1 ± 8.8 months for patients with stable disease and 10.5 ± 6.8 months for patients not responding to AGT plus HC. Therapy was well tolerated with toxicities including lethargy (16%), rash (9%), nausea (12%), and edema (18%). Clinical findings of adrenal insufficiency were documented in four cases (5%).

Adrenal Steroid Levels. Of the 129 patients enrolled on study, a complete serum steroid level profile of 4 samples was obtained in 69 (53%) and a base-line and at least one follow-up study after 2 months or more of AGT plus HC therapy was obtained in 94 (73%) of study entrants. Fig. 1A displays a linear regression of base-line testosterone and Fig. 1B displays base-line AND levels as a function of age in these castrated men. The slopes of the generated lines for these adrenal androgens were not significantly different from zero. Hence, in these castrated men, adrenal production of these androgens showed no trend to decline with age.

Figs. 2 and 3 display serial median DHEA-S and AND levels, respectively, from the 69 patients in whom a complete, 3-month steroid level profile was obtained. Using a two-sided Wilcoxon signed rank test adjusted for ties and zeroes, the fall in the median DHEA-S level was significant with P < 0.001, whereas the change in median AND levels was not significantly altered by our therapy. The suppression of median base-line testosterone, DHT, and FT levels were 9 ng/dl, 6.0 ng/dl, and 0.8 pg/ml, respectively, with values after 12 weeks of therapy falling to median levels of 6.5 ng/dl, 5.0 ng/dl, and 0.7 pg/dl.

Table 1 displays the effects of 2 to 3 months of therapy with AGT plus HC on mean adrenal steroid levels. This larger population (up to 94 patients) includes 25 patients who developed progressive disease after only 2 months of therapy, were removed from study and, hence, did not complete the entire 3-month protocol as did the 69 patients shown in Fig. 1. While DHEA-S levels fell in 87% of this larger group, close to 50% of patients had increases in AND, testosterone, DHT, and FT levels while on AGT plus HC, with the largest changes seen in AND levels.

Fig. 4 displays linear regression analyses of the relationship of AND and testosterone levels after 1 month (Fig. 4A), 2
ACT AND ADRENAL STEROID LEVELS

Table 1 Adrenal steroid levels before and after aminoglutethimide plus hydrocortisone therapy

<table>
<thead>
<tr>
<th>Overall effect</th>
<th>DHEA-S (µg/dl)</th>
<th>AND (ng/dl)</th>
<th>Testosterone (ng/dl)</th>
<th>DHT (ng/dl)</th>
<th>FT (pg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>94</td>
<td>92</td>
<td>93</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Base line (mean ± SD)</td>
<td>48.2 ± 50.8</td>
<td>44.7 ± 36.1</td>
<td>10.9 ± 6.4</td>
<td>7.2 ± 3.9</td>
<td>1.0 ± 1.0</td>
</tr>
<tr>
<td>On therapy*</td>
<td>13.4 ± 18.7</td>
<td>104.2 ± 185.8</td>
<td>6.4 ± 22.6</td>
<td>6.3 ± 4.0</td>
<td>1.3 ± 1.2</td>
</tr>
<tr>
<td>Steroid reduction</td>
<td>82 (87%)</td>
<td>48 (52%)</td>
<td>46 (49%)</td>
<td>49 (55%)</td>
<td>47 (54%)</td>
</tr>
<tr>
<td>No. (%)</td>
<td>12 (13%)</td>
<td>44 (48%)</td>
<td>47 (51%)</td>
<td>40 (45%)</td>
<td>40 (46%)</td>
</tr>
<tr>
<td>Base line (mean ± SD)</td>
<td>53.8 ± 51.8</td>
<td>47.7 ± 38.6</td>
<td>12.8 ± 7.0</td>
<td>8.5 ± 4.3</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>On therapy</td>
<td>12.9 ± 18.3</td>
<td>17.6 ± 13.6</td>
<td>4.4 ± 3.4</td>
<td>4.9 ± 1.8</td>
<td>0.6 ± 0.4</td>
</tr>
<tr>
<td>Steroid elevation or no change</td>
<td>9.8 ± 13.8</td>
<td>41.7 ± 33.4</td>
<td>9.0 ± 5.2</td>
<td>5.6 ± 2.5</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>No. (%)</td>
<td>16.8 ± 21.9</td>
<td>190.4 ± 234.3</td>
<td>23.9 ± 29.0</td>
<td>7.9 ± 5.1</td>
<td>2.1 ± 2.2</td>
</tr>
</tbody>
</table>

* On therapy, after 8 to 12 weeks of aminoglutethimide plus hydrocortisone.

Fig. 4. A, a linear regression analysis of testosterone and AND levels after 1 month of ACT plus HC therapy; B, a linear regression analysis of testosterone and AND levels after 2 months of ACT plus HC therapy; C, a linear regression analysis of testosterone and AND levels after 3 months of ACT plus HC therapy.

DISCUSSION

These endocrine studies demonstrate several findings. First, in castrated men androstenedione and testosterone levels do not appear to decrease with age. Other investigators have noted age related declines in DHEA-S levels but conflicting data have been published regarding the effect of age in AND levels (16, 17). Second, in the doses studied, ACT plus HC does influence adrenal steroid synthesis. In 87% of patients, DHEA-S levels were reduced to the lower detection limits of the RIA. The overall effect observed on AND, testosterone, DHT, and FT was toward lowered levels. However, the effect on these steroids was variable with up to 34% of patients actually experiencing a doubling or more in their base-line AND levels. And finally, while there was a trend for patients with a doubling or more of base-line AND levels to have a reduced incidence of a clinical response to ACT plus HC therapy, this association was not significant.

The effect of ACT plus HC on adrenal androgen levels was unclear. In postmenopausal women this drug alone failed to lower testosterone and DHT levels and has had variable effects in AND levels (10, 11). The ability of ACT plus HC to suppress AND, testosterone, and DHT in castrated men has been suggested by others in smaller series (18, 20). It may be that AGT plus HC affects adrenal steroid synthesis differently in men than in women.

We monitored adrenal steroid levels for only the first 3 months of AGT plus HC therapy. It has been suggested that in postmenopausal women with breast carcinoma the acute effects of AGT plus HC on adrenal steroid synthesis differ from the chronic effects (21). It is uncertain whether the variable effects on AND and other adrenal androgen levels reflect a stable state
or rather is a transitory phenomenon. While our study called for a morning collection time, an additional potential factor in the way in steroid levels is the temporal periodicity of adrenal steroid production. Possible explanations for a rise in AND and other androgen levels in some patients include a lack of patient compliance, effects of AGT plus HC on prolactin, or inadequate suppression of ACTH by 40 mg/day of HC. A differential effect of ACTH on various steps in adrenal steroid synthesis had been recognized (22) and prolactin has been suggested by some workers to directly influence adrenal androgen secretion (23). Only by long term monitoring of prolactin, ACTH, and other pituitary axis hormones, as well as adrenal steroids, will the mechanism of the rises in AND and other adrenal androgens be clearly understood.

Of concern is the potential clinical effect of actually increasing body androgen production in some patients with metastatic prostatic carcinoma treated with AGT plus HC. Although prostate cancer eventually progresses after an orchietomy, there is significant evidence to suggest that these tumors remain sensitive to androgen stimulation (1). Marked symptomatic progression has been documented in most patients receiving exogenous testosterone either as an adjunct to $^{32}P$ therapy (24) or when given as a cell synchronization maneuver prior to the administration of cytotoxic chemotherapy (25). It is possible that the clinical efficacy of AGT plus HC in castration resistant prostatic carcinoma could be enhanced by the achievement of significant adrenal androgen suppression in all patients. The best method to accomplish this has yet to be determined.

APPENDIX A: AMINOGLUTETHIMIDE STUDY GROUP MEMBERS

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