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ENDOCRINE EFFECTS OF AMINOGLUTETHIMIDE (Ag) PLUS HYDROCORTISONE (HC) VERSUS HIGH DOSE OF HYDROCORTISONE IN POSTMENOPAUSAL BREAST CANCER.

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In 16 patients with metastatic breast cancer we compared changes in plasma steroid levels during 3 days treatment with 40 mg HC followed by addition of 1000 mg Ag (group A,n=8) or by doubling of the dose to 80 mg HC (group B,n=8)

Effects of 40 mg HC orally during 3 days ($\bar{X}$± S.D.,n=16):

Parameter	Before treatment	After 3 days 40 mg HC:
DHEA-S µmol/l	0.34 ± 0.35	0.17 ± 0.19 (p< 0.05)
A'dione nmol/l	2.56 ± 1.95	1.09 ± 0.69 (p< 0.01)
Estradiol pmol/l	29.1 ± 14.3	21.8 ± 6.7 (p< 0.05)
Cortisol 8.oo	501 ± 145	625 ± 183 (p< 0.05)
" 16.oo nmol/l	345 ± 169	534 ± 199 (p< 0.01)

Prolonged treatment with 80 mg HC caused further suppression of androgens,while E_2 remained unchanged.The addition of Ag to HC had no significant effect on E_2 levels.The main difference between the 2 groups was in the level of androgens.

Effects of 80 mg HC vs 1000 mg Ag plus 40 mg HC ($\bar{X}$ ±S.D.n=8):

Parameter	Before treatment		After 6 weeks of treatment:	
	Group B	Group A	80 mg HC(B)	40 mg HC+Ag (A)
DHEA-S	0.41±0.38	0.27±0.32	0.09±0.09	0.01±0+*
A'dione	3.08±2.46	2.04±1.20	0.58±0.46	1.01±0.56 (n=5)
Estradiol	27.4±14.5	30.9±14.8	24.1±11.9	18.3±9.1 (n=6)
Cortisol 8.oo	549±155	454±125	691±464	424±306 (n=6)
SHBG nmol/l	88.5±59.4	65.0±14.5	66.0±27.3	98.3±20.7*+

*p <0.05 between groups A and B +p<0.05 vs day 0

In conclusion: HC alone has marked effects on the peripheral endocrine environment but addition of Ag caused more pronounced suppression of DHEA-S and E_2/SHBG ratios.

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TREATMENT OF POSTMENOPAUSAL ADVANCED BREAST CANCER WITH LOW-DOSE AMINOGLUTETHIMIDE

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In a phase II study, 42 evaluable patients (pts) with advanced progressive breast cancer (BC) were treated with low-dose aminoglutethimide (AG) (2 x 250 mg per day) without hydrocortisone (HC) supplementation.
Median age of the pts was 59 years (range, 40-79) and median Karnofsky performance status was 80% (range,70-100%). Partial remissions (PR) were observed in 10 pts (24%) with a median duration of 11 (range,1-19) months and disease stabilisations (NC) in 14 pts (33%) lasting 1-21 (median 6) months. Bone metastases responded well with 69% PR and NC, whereas locoregional and pleuropulmonal metastases showed disease progression in 56% and 61% of the pts, respectively. Pts with positive receptor status achieved 36% PRs and pts with unknown receptors 15% PRs. Of 2 pts with negative receptors, 1 showed PR, 1 progressive disease. Side effects (drowsiness, ataxia, rash) were mostly mild and transient and did not require drug discontinuation. In 70% of the pts no side effects were observed. Serum estradiol decreased significantly whereas cortisol levels remained unaltered. It is concluded that low-dose AG is as efficient as conventional-dose AG in terms of both remission rates and remission duration in postmenopausal BC. Dose reduction significantly decreases incidence and degree of side effects. HC supplementation is not mandatory.

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ANDROGEN SUPPRESSION BY HYDROCORTISONE WITHOUT AMINOGLUTETHIMIDE IN ORCHIDECTOMISED MEN WITH PROSTATE CANCER

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Patients with advanced prostatic cancer benefit from bilateral orchidectomy, but all eventually relapse. Aminoglutethimide (AG) can produce a second remission; this therapeutic effect is attributed to suppression of androgens of adrenal origin which act as growth factors in prostate cancer. Suppression of adrenal androgens is accentuated by the addition of physiological replacement doses of hydrocortisone (HC). The question arises as to whether doses of HC sufficient to suppress ACTH would also suppress adrenal androgens in a manner similar to that seen with AG.
Six men who had relapsed following orchidectomy were studied during treatment with HC (30 mg daily for one month) followed by HC + AG (30 mg HC/750 mg AG daily for one week). Blood was taken and stored at -20° prior to RIA for testosterone (T), sex hormone binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS), and androstenedione (A4). The significance of the difference in the mean levels was assessed by Student's 'T' test.
Serum T and DHEAS fell significantly (p<0.005) from pre-treatment levels in all six patients receiving HC. Serum A4 and SHBG fell (p<0.05) in 4/6 and 5/6 patients respectively with HC. The regimen of HC + AG reversed the suppression of serum T (p<0.01), DHEAS (p<0.05), SHBG (p<0.01); changes in A4 were not significant.
It is concluded that AG has no therapeutic indications in prostate cancer and that physiological doses of HC represent the best second hormonal manoeuvre for such patients.

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ADRENAL BLOCKADE WITH AMINOGLUTETHIMIDE IN PROSTATE CANCER.

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The optimum treatment for patients with advanced prostatic cancer who have relapsed following a remission to, or failed to benefit from orchidectomy or oestrogen treatment is uncertain. We present here results of treatment with aminoglutethimide (A/G) (250mg tds) and physiological steroid replacement, cortisone acetate (37.5mg/day) in 127 men (median age 69 years range 50-89) with advanced prostatic cancer which was resistant to orchidectomy and/or oestrogen therapy. Classification of response was according to NPCP criteria. All patients had had a prior orchidectomy and/or oestrogen therapy and all patients had actively progressing symptomatic disease. Most had also had prior radiotherapy. Twenty (16%) patients had an objective remission while 27 (21%) had stabilization of previously progressing disease. Performance status (ECOG) significantly improved in these groups while it significantly decreased in the group with progressive disease. Mean survival was significantly longer (p 0.001) in the remitters (16.2 months) and the static group (8.5 months) than in the patients who failed to benefit (4.7 months). Side effects were minimal and the drug was ceased because of toxicity in only one patient.

Conclusions

1. Adrenal blockade with A/G and steroid replacement is a safe and useful treatment in patients with advanced prostatic cancer who have failed standard therapy.
2. Approximately 37% of patients have an improvement in performance status and survival.
3. Earlier treatment with A/G might lead to better results and warrants investigation.