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Aromatase inhibition with low dose aminoglutethimide in the treatment of breast cancer.

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Aminoglutethimide (A/G), which inhibits adrenal steroid synthesis when given in combination with physiological cortisone replacement, has been shown to be a potent inhibitor of aromatase, (which converts androgens to oestrogens) in vitro.[1] In this study the efficacy of low dose (LD) A/G (125mg bd) without steroid replacement was determined in post menopausal women with actively progressing advanced breast cancer (BC). Some women who failed to respond to LD A/G, or who responded and then relapsed were then treated with conventional dose (CD) (250mg bd or tds) and steroid replacement. Of 135 women (median age 65 years range 37 - 90) with LD A/G, 36 (27%) had an objective remission while a further 12 (9%) had stabilization of previously progressing disease. (UICC criteria). Fifty of the non responders, 8 of the responders and 7 of the static group were changed to CD A/G and steroids with progressive disease. 11 of these 65 patients (17%) then had an objective response while arrest in disease occurred in a further 5 (8%). Plasma androgens (DHEA-SO_4 and Testosterone) did not alter significantly in patients with LD A/G but fell in patients changed to CD A/G and steroid replacement. Toxicity was minimal, although 2 patients on LD A/G developed signs of adrenal insufficiency.

Conclusions

1 LD A/G is effective in advanced B/C possibly due to inhibition of aromatase activity.
2 LD A/G has no effect on adrenal androgen synthesis, while CD A/G and steroid replacement lowers DHEA-SO_4 and testosterone.
3 The two treatments do not produce identical results as some patients who fail LD subsequently respond to CD and steroid replacement.

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IN VIVO TESTING OF IRREVERSIBLE AROMATASE INHIBITORS IN THE RAT.

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The growing interest in the field of aromatase inhibitors as selective antitumor agents for estrogen-dependent tumors led us to develop a method for in vivo evaluation of aromatase inactivation in the rat. 4-hydroxyandrostenedione (4-OHA),a known irreversible aromatase inhibitor, was used as standard for method testing. Data were compared with antitumor effects on DMBA-induced rat mammary ca. Rat ovarian aromatase activity (OAA) can be increased by PMSG. The influences on OAA of the number (N) and frequence of PMSG (100 IU/rat s.c.) injections and of the time interval (TI) between the last PMSG and killing were studied. Ovarian microsomes were isolated and OAA measured according to Thompson and Siiteri. OAA increased with increase of N, but two treatments at 96h interval with a TI=96h proved sufficient for an effective stimulation. In such PMSG-treated rats 4-OHA given 24h before killing at doses of 3, 10 and 30 mg/kg s.c. reduced microsomal OAA in a dose-related manner reaching 75% inhibition at 30 mg/kg. Oral treatment was less effective: only 30% inhibition was observed after 100 mg/kg. DMBA-induced tumor bearing rats were given 4-OHA 8, 20 and 50 mg/kg s.c. and up to 125 mg/kg p.o. 5 times/wk for 4 wks.Tumor regressions were observed after s.c.(23%,34%,60%) but not after oral treatment. The results indicate that the PMSG stimulation model described allows a rapid and reliable testing of in vivo irreversible aromatase inhibition: a positive correlation between enzyme inactivation and antitumor activity was found for 4-OHA.

REFERENCE: Thompson, E. A. Jr. and Siiteri, P.K. J. Biol. Chem. 249, 5364 (1974).