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SUPPRESSION OF PLASMA ANDROGENS BY SPIRONOLACTONE IN CASTRATED MEN WITH CARCINOMA OF THE PROSTATE

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ABSTRACT

Spironolactone, an inhibitor of androgen synthesis, has been administered to castrated men with metastatic carcinoma of the prostate. Plasma levels of testosterone, androstenedione and dehydroepiandrosterone were significantly decreased. These data indicate that spironolactone suppresses adrenal androgen production and suggest that it may be of benefit in the treatment of orchiectomized patients with advanced carcinoma of the prostate.

Bilateral adrenalectomy and hypophysectomy have been used for the palliative treatment of men with carcinoma of the prostate who have reactivation of metastatic disease after castration or estrogen therapy. To achieve this effect with medical treatment cortisone has been used to suppress adrenocorticotropic hormone secretion and antiandrogens have been administered to block the effect of circulating androgens at target organ receptors. We have evaluated an inhibitor of androgen synthesis, spironolactone, for its ability to suppress adrenal androgen production.

Spironolactone, a steroidal aldosterone antagonist, frequently produces gynecomastia and impotence in treated men.[1, 2] Preliminary data indicate that spironolactone suppresses plasma testosterone and androstenedione levels in normal men and in vitro inhibits the 17, 20-lyase and possibly other enzymatic steps in androgen synthesis.[3] Based on these findings we have tested the ability of spironolactone to lower plasma testosterone, androstenedione and dehydroepiandrosterone levels in castrated men with metastatic carcinoma of the prostate.

METHODS

Seven men between 46 and 78 years old with metastatic carcinoma of the prostate previously treated with estrogens and bilateral orchiectomy were studied. Base line blood samples were collected on 3 consecutive days prior to therapy. Men receiving 100 mg. spironolactone per day had samples collected after 1 week (3 men), 2 to 3 weeks (3 men) and 4 to 7 weeks (1 man). Samples were drawn on patients receiving 400 mg. per day after 1 week (4 men), 2 to 3 weeks (3 men) and 4 to 7 weeks (2 men). All samples were drawn at 8 a.m. and were permitted to clot at room temperature prior to centrifugation. Serum was stored at minus 20C until assayed. Plasma testosterone, androstenedione and dehydroepiandrosterone were measured by a competitive enzyme method described previously.[4] Serum creatinine, electrolytes, acid phosphatase and blood urea nitrogen determinations were performed on all patients. Statistical significance was analyzed by the Mann-Whitney U test.

RESULTS

Prior to treatment with spironolactone the concentration of plasma testosterone was 0.45 plus or minus 0.06 ng. per ml. plus or minus standard error of mean, plasma androstenedione was 1.1 plus or minus 0.2 ng. per ml. and plasma dehydroepiandrosterone was 2.5 plus or minus 0.3 ng. per ml. These values for androstenedione and dehydroepiandrosterone fall within the range of normal values reported by Migeon.[5] After therapy with spironolactone the plasma levels of all 3 androgens were significantly lower (p less than 0.05) (see figure). This effect, which was more apparent after 2 to 3 weeks of treatment, was most marked for testosterone and was of equal magnitude with both doses of spironolactone.

One of 3 men receiving 100 mg. spironolactone per day and 2 of 4 men receiving 400 mg. per day experienced relief of pain for 4 to 10 weeks. In the man with the longest remission of symptoms serum acid phosphatase levels decreased from 4.0 to 4.9 I.U. per ml. to 3.2 to 3.7 I.U. per ml. Treatment with 400 mg. spironolactone per day was discontinued in 2 men in whom hyperkalemia developed (serum potassium 6.6 and 7.0 mEq. per l.). Both patients had pre-existing renal disease and had elevated serum creatinine levels prior to treatment.

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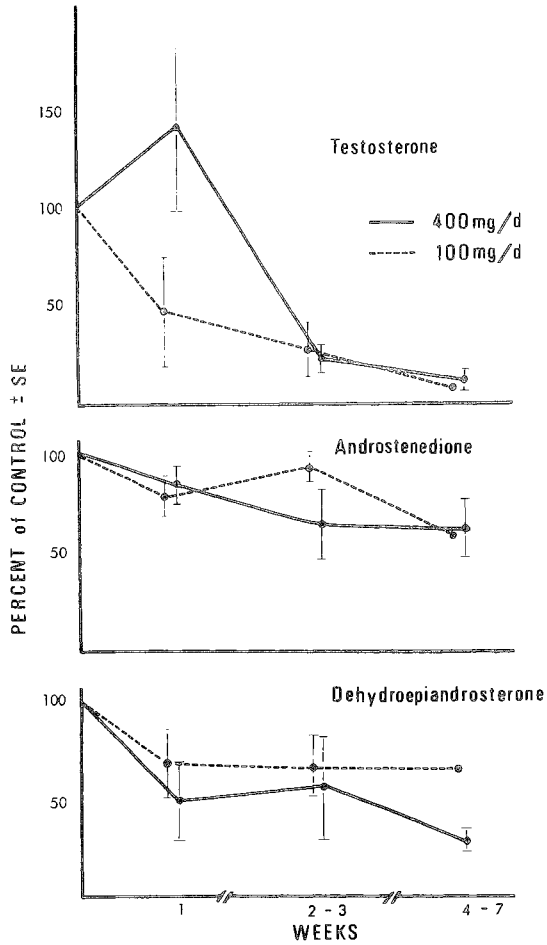

Effect of spironolactone on plasma levels of testosterone, androstenedione and dehydroepiandrosterone in orchiectomized men with carcinoma of prostate.

DISCUSSION

Because the testes are the major site of testosterone synthesis plasma testosterone falls to low levels after bilateral orchiectomy. Although the early studies of Scott and Vermeulen suggested that after orchiectomy there was a late increase in adrenal androgen production, these studies were based on the urinary excretion of total 17-ketosteroids.[6] It is now recognized that these elevations are not specific for androgenic metabolites and are caused by anxiety, pain and stress. With the development of sensitive techniques for the measurement of plasma levels of testosterone, it has been shown that plasma testosterone levels are decreased by 90 per cent after bilateral orchiectomy and that there is no late rise in plasma testosterone levels.[7, 8] In this study we have demonstrated that there is also no late elevation of androstenedione or dehydroepiandrosterone.

After therapy with spironolactone plasma levels of testosterone, androstenedione and dehydroepiandrosterone fall due to suppression of adrenal androgen synthesis. Spironolactone, additionally acting as an antiandrogen, may also inhibit the effect of androgen at target tissues.[9-11] These data suggest that spironolactone may be of benefit in the treatment of orchiectomized patients with advanced carcinoma of the prostate. In studies of another antiandrogen, cyproterone acetate, symptomatic improvement has been demonstrated in 50 to 60 per cent of previously treated men with metastatic carcinoma of the prostate.[12, 13] Although these forms of therapy are by no means curative they occasionally provide excellent palliation.

Hyperkalemia is a major hazard of spironolactone therapy and the drug should not be administered to patients with diminished renal function. It is important to review the patient's dietary habits and medications before treatment is initiated and to monitor serum potassium concentrations closely early in the course of therapy. The patient should be advised to avoid excessive intake of food high in potassium.

Another agent, aminoglutethimide, has been demonstrated to suppress adrenal androgen synthesis.[14] However, because this drug inhibits the side chain cleavage of cholesterol and subsequent hydroxylation, it also blocks the synthesis of cortisol and aldosterone.[15] Patients treated with aminoglutethimide must receive glucocorticoid replacement and should be observed for the development of hypothyroidism.

In conclusion, spironolactone effectively lowers plasma androgen levels in castrated men. Until a more potent, safe, selective inhibitor of androgen synthesis becomes available, spironolactone should continue to be evaluated in the management of patients with advanced carcinoma of the prostate.

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