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Letter to the Editor

Oral High-dose Medroxyprogesterone Acetate Causes Adrenal Suppression in Patients with Breast Cancer

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TREATMENT with oestrogens or androgens in patients with disseminated breast cancer can cause troublesome side-effects [1]. This has caused renewed interest in the use of progestational compounds. Parenteral treatment in high dose may result in a remission rate similar to that achieved with tamoxifen [2].

MPA is bound by progesterone receptor-positive tumours *in vitro* [3]. Data from Sweden and Italy have shown 30% remission rates, preferentially in soft tissue, nodal and lung metastases [4, 5]. While MPA in most cases has been administrated intramuscularly, high oral doses result in comparable serum levels measured by radioimmunoassay [6].

Suppression of adrenal function by inhibition of ACTH release by this compound has been demonstrated, but has not been recognised as a possible cause of complications in these patients [7–10]. The Cushingoid appearance and the persistent listlessness of some patients after withdrawal of MPA prompted us to investigate the severity of adrenal suppression.

The median cortisol level was measured by RIA in 13 patients using 900 mg MPA daily for more than 6 weeks. It was as low as 40 nmol/l (range, 0–205; normal range, 300–750 nmol/l), while ACTH levels (RIA) were also depressed in all patients (median value below detection limit, range, 0–56 ng/l; normal range, 70–700 ng/l).

Despite these low cortisol levels, mean body weight increased by 6% and blood pressure by 24/14 mm Hg, while no electrolytic abnormalities were found. Adrenal suppression may well be the most important effect of this compound, as cortisol and androgen metabolites were virtually absent from urinary steroid spectra. Serum androstenedione concentrations were low (median value, 1.0 nmol/l; range, 0.55–1.55; normal postmenopausal range, 1.5–3.5 nmol/l). This could mean that MPA is as effective as aminoglutethimide in suppressing adrenal function. However, side-effects of MPA are considerably less and additional ACTH suppression with cortisone is not necessary [11]. The effect on ACTH is thought to be exerted by a 21-hydroxylated metabolite [12]. The location for 21-hydroxylation is unknown, as it occurs in adreno-ovariectomized patients as well [12], while 21-hydroxylation by liver tissue is known not to be possible.

In conclusion, MPA or its metabolites interfere with ACTH release, causing adrenal suppression. Evidently, the existing serum levels of MPA are an adequate replacement for the missing steroids, but it is not certain that their corticoid potency is sufficient during stress. When this drug has been used for longer periods, the possibility of prolonged adrenal suppression after its withdrawal must be kept in mind. Adrenal suppression by MPA could well represent its main therapeutic effect in postmenopausal patients with breast cancer.

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