The Antiinflammatory Properties of Medroxyprogesterone Acetate

To the Editor:

I have read the article by Wakatsuki et al1 with considerable interest. The study showed that the continuous oral treatment of postmenopausal women for 3 months with conjugated equine estrogens (CEE) (0.625 mg/day) alone or with medroxyprogesterone acetate (MPA) at the dose of 2.5 mg/day, significantly increased serum C-reactive protein (CRP) and amyloid A protein (SAA) levels. This effect was attenuated by the concurrent administration of MPA at the dose of 5 mg/day. CEE alone significantly decreased the concentration of E-selectin, but the concentrations of intracellular adhesion molecule (ICAM-1) and vascular cellular adhesion molecule (VCAM-1) did not change significantly. Concentrations of ICAM-1, VCAM-1, and E-selectin were all significantly reduced among postmenopausal women treated with CEE plus MPA 5 mg/day.

The authors conclude that because androgens have antiinflammatory properties,2 androgenic progestins such as MPA (?) may attenuate proinflammatory effects of estrogens and may actually be responsible for the favorable effect of estrogen-progestogen combinations on inflammatory markers such as cellular adhesion molecules (ICAM-1, VCAM-1, E-selectin) and acute phase proteins (CRP and SAA) in postmenopausal women undergoing hormonal replacement therapy.

MPA is a 17α-hydroxyprogesterone derivative and it is structurally related to progesterone and not testosterone.3 In addition to binding to progesterone receptor, MPA may interact with the glucocorticoid receptor.4 Progesterone and its derivatives have antiinflammatory and immunosuppressive properties that are relevant for maintenance of pregnancy.5 Because MPA is not a 19-nortestosterone derivative (androgenic progestin), its antiinflammatory properties can be attributed to its ability to interact with the progesterone and glucocorticoid receptors, not the androgen receptor.

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Response

Dr Rachoni pointed out that the antiinflammatory effect of medroxyprogesterone acetate (MPA) on plasma inflammatory markers, such as C-reactive protein and serum amyloid A protein, may not be related to the androgenic effect of MPA. Because MPA is a 17α-hydroxyprogesterone derivative and binds progesterone and glucocorticoid receptors with a high affinity, we agree with his suggestion, in part, that its antiinflammatory properties may be attributed to its ability to interact with the progesterone and glucocorticoid receptors. According to Bentel et al,1 however, MPA may also have an androgenic effect by activating androgen receptor–regulated pathways. In addition, Labrie et al2 have demonstrated that the androgenic effect of MPA may have favorable effects in breast cancer subjects, comparable to other endocrine therapies, including tamoxifen. Therefore, MPA seems to have actions similar to those of testosterone derivatives. Testosterone derivatives have antiinflammatory effects and adverse effects on lipids and endothelial function.

We previously demonstrated that clinical doses of MPA may offset estrogen’s favorable effects on high-density lipoprotein cholesterol and endothelial function in postmenopausal women.3 In contrast, the addition of micronized progesterone, which has less androgenic effect than MPA, does not attenuate those favorable effects of estrogen.4 The impact of MPA on these parameters may be related to its androgenic potency. Based on these findings, androgenic properties of MPA may be responsible for the reduction in plasma inflammatory markers.5 Further studies are needed to determine the precise mechanism of the antiinflammatory effect of MPA.

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