

Letter to the Editors

Importance of the progestogen added to the estrogen in hormone therapy

The results of the Women's Health Initiative (WHI) study were not representative of current medical practice because the subjects were treated without indication, were far too old for replacement and not completely healthy.

Another important point of criticism, and a reason for doubting the results that is given too little weight in the critical analysis of the WHI trial, is that the preparation used (conjugated equine estrogens 0.625 mg + medroxyprogesterone acetate (MPA) 2.5 mg) is inappropriate for the intended purpose of the trial, being ineffective for primary and secondary prevention of cardiovascular disease. The progestogen MPA seems to be one important reason for some serious side-effects. These conclusions about MPA became compelling when the further publications showed that the results of the estrogen-only arm gave a better outcome and with fewer complications than the estrogen/progestogen arm. It appears logical, therefore, that the unfavorable data and some of the unwanted events in the estrogen/progestogen arm could be attributable to the combination with MPA, especially in the combined continuous form of medication. The daily addition of oral MPA to the estrogen could probably counteract some of the positive estrogen effects day by day.

We know that MPA is antiestrogenic, slightly androgenic and acts as a corticosteroid by its binding to the corticosteroid receptor. The main reasons for the failure in prevention and for the significant unwanted side-effects in the estrogen/progestogen arm of WHI (besides inappropriate study design) are probably the following well-documented pharmacological qualities of the progestogen MPA, which apparently were not known or considered by the designers of the WHI study:

- (1) MPA (combined with conjugated estrogens) has unfavorable effects on levels of serum high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and lipoprotein(a)¹, as compared to estrogen monotherapy, especially in the combined continuous form.
- (2) MPA decreases the estrogen-induced perfusion of coronary arteries², of cerebral vessels³, and enhances a vasoconstrictor response⁴.
- (3) MPA neutralizes the antiatherosclerotic effect of estrogens in the castrated cynomolgus monkey^{5,6}. This attenuating effect is not seen after the addition of progesterone⁶.
- (4) MPA stimulates the proliferation of smooth coronary muscle cells and therefore attenuates the favorable antiproliferative vascular effect of estrogens on the functional and organic processes, which are important for the development of atherosclerosis. MPA inhibits chemokinin and the monocyte attraction protein, which are essential for preatherosclerotic changes of the vessels⁷.
- (5) In rabbits, MPA tends to cause an increase in arterial tension, an ischemic vasoreaction and a diminished cardiac and cerebral vasodilatory response⁸. This effect can be partly balanced by conjugated estrogens. Clinically, there are indications that this effect may induce an increase in blood pressure in predisposed patients during conjugated estrogen + MPA medication. These results need re-evaluating. In contrast, progesterone may even promote vasodilatation and protect against vasospasms².
- (6) The incidence and the mortality of stroke seem to be slightly higher in combination therapy with MPA as compared with estrogen monotherapy (e.g. WHI). This finding also needs validation.
- (7) MPA exerts a thrombogenic action *in vitro* by upregulation of the thrombocyte receptor and the tissue factor in the vessel walls⁹. Clinically, the relative risk for thromboembolism is higher in the WHI study with the combination of conjugated estrogens + MPA (hazard ratio 2:11) than with conjugated estrogens alone (hazard ratio 1:33).

- (8) MPA increases glycogenesis and can attenuate the insulin sensitivity and may, in some long-term treated persons, induce a metabolic syndrome with hyperinsulinemia and insulin resistance¹⁰⁻¹². These metabolic effects were also produced experimentally by MPA addition to conjugated estrogen in the cynomolgus monkey¹³ and are known to be relevant for the development of type II diabetes.
- (9) MPA (together with estrogen) causes hyperproliferation of breast epithelium in the cynomolgus experiment¹⁴ and in female patients treated with oral conjugated estrogens + MPA⁷. Moreover, addition of MPA has been found to stimulate estrone sulfatase¹⁵ and 17-hydroxysteroid dehydrogenase in human breast tissue¹⁶, so that the concentrations of estradiol and estrone within the breast are increased by the addition of oral MPA in predisposed women. Further potentially detrimental effects of MPA upon the breast could be mediated by a decrease of sex hormone binding globulin, by an increase of IGF-1 and a decrease of IGF-binding protein-3 by MPA¹⁷. Addition of MPA to estrogen apparently also clinically increases the incidence of breast cancer. Moreover, estrogen + MPA causes a greater increase in radiological breast density and breast symptoms than, for example, estrogen + norethisterone¹⁸.

The results of the WHI study suggest that the combination of conjugated equine estrogens 0.625 mg + MPA 2.5 mg given continuously, as used in the WHI study and the Heart and Estrogen/

progesterin Replacement Study (HERS) is not suitable for long-term primary or secondary prevention of cardiovascular disease. This special preparation (not to be compared to other preparations) may, moreover, cause several worrying unwanted side-effects in some patients. Because the risk/benefit ratio of this estrogen/MPA combination is not positive, its further use in HT, especially for long-term use, should be considered critically. Apparently, the sequential addition of MPA to estrogen exerts less detrimental effects, as estrogens in sequential preparations are at least acting unhampered during the first 14 days of the treatment cycle. Oral hormone therapy as used in the WHI study is apparently not the 'gold standard' for women in the late postmenopause years. Primary oral medication in older women (> 60 years), as used in the WHI study, is relatively contraindicated. Local or parenteral medication with estrogen in low doses is to be preferred in such late postmenopausal cases. Progesterone and the different progestins have different effects and side-effects. According to the evidence available, it is apparent that the selection of the progestogen in HT deserves special care and should probably be restricted to genuine progesterone or to progestogens similar to progesterone, which should in any case be free of relevant unwanted side-effects. The accepted rule so far to add a progestogen to the estrogen in all pre- and postmenopausal women with a uterus should, in the light of the WHI study and the findings summarized here, be newly formulated and depend upon the individual and her medical advisor.

Ulm
Germany

C. LAURITZEN

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