Kloosterboer, HJ.

Tibolone: a steroid with a tissue-specific mode of action.

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From the Research and Development Laboratories, NV Organon, P.O. Box 20, 5340, Oss, The Netherlands.

In postmenopausal women tibolone has proved to prevent bone-loss and relieve climacteric symptoms as effectively as estrogens, but it does not stimulate the endometrium and the breast. This clinical profile strongly suggests that tibolone is a compound with tissue-specific action. Tibolone is quickly metabolized into its main active metabolites, 3alpha and 3beta-OH, which are also present in an inactive, sulphated, form. In addition a Delta4-metabolite is found in circulation. The 3-OH-metabolites bind only to the estrogen receptor while the Delta4-isomer shows affinity only to the progesterone and androgen receptors. Tibolone prevents bone loss in a similar way to estrogens. Studies on bone mass using anti-estrogen, antiprogestin and anti-androgen in combination with tibolone, confirmed the sole involvement of the estradiol receptor. Increases in skin temperature as well as vaginal atrophy can be prevented by tibolone in a similar way to estrogens. Breast safety studies showed that tibolone clearly inhibited the growth of tumors in a DMBA model. In breast cell lines, tibolone profoundly inhibited sulphatase activity and an increase in apoptosis and decrease in cell proliferation was found. The stimulation of the endometrium is prevented by the local formation of the Delta4-isomer from tibolone or the 3beta-OH-metabolite. We conclude that tibolone acts as a tissue-specific compound by mediating its effects via steroid receptors and enzymatic pathways. This dual effect of tibolone explains its positive clinical effects on bone, vagina and brain, and avoids stimulation of the endometrium and breast tissue.

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