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Endocrine prevention of breast: any role for tibolone?

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1. Introduction

Tibolone is a steroid with a 3-keto-5-10 configuration in the A-ring and a 7α-methyl substitution in the B-ring which give tibolone its unique properties. After oral administration, three metabolites are found in circulation; 3α- and 3β-hydroxytibolone and a 3-keto-Δ4 isomer. The hydroxy metabolites only bind to the oestradiol receptor, while the Δ4 isomer and tibolone do not, but bind to the progesterone and androgen receptors. The hydroxy metabolites have a half-life of approximately 7 h and tibolone and the Δ4 are found in the circulation for a short period after administration. Approximately 80% of the hydroxy metabolites are found in the circulation in an inactive, sulphated form.

Tibolone shows tissue-specific effects in postmenopausal women due to the regulation of receptor activities in various relevant tissues which is determined by tissue-specific changes in steroid metabolising enzymes. Tibolone expresses oestrogenic effects on bone, vagina and brain, whereas the endometrium is not stimulated. In the endometrium, the progestagenic metabolite is locally formed and prevents oestrogenic stimulation. This leads in most women to an atrophic endometrium.

The effect of tibolone on the breast was extensively investigated in preclinical studies in order to assess tibolone's safety. Both the oestrogenic and progestagenic properties of tibolone may increase the risk of breast cancer and therefore a better insight on the effect of tibolone on the breast is needed.

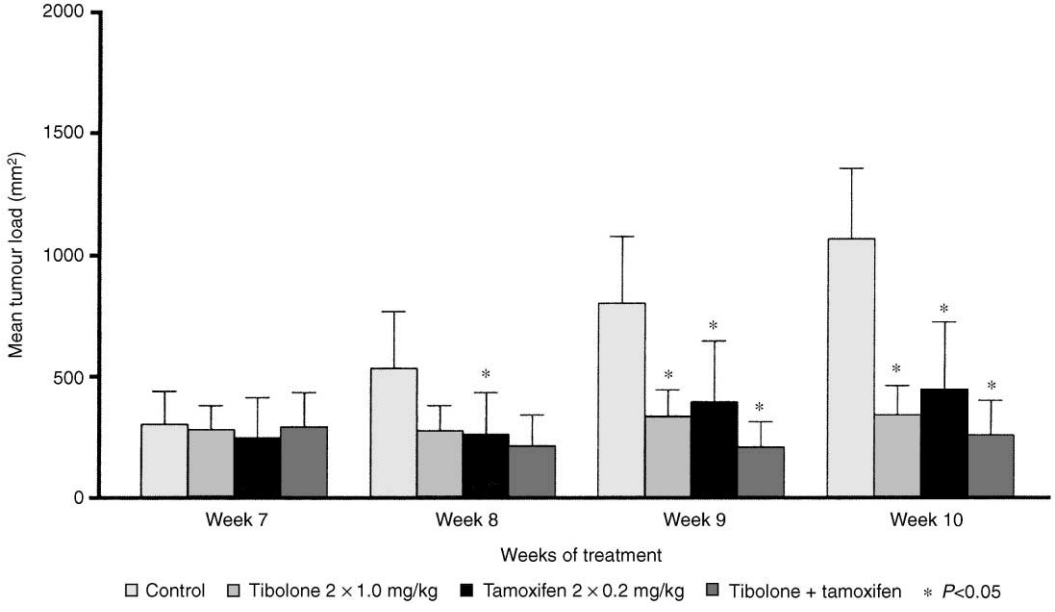

Fig. 1. Effect of tibolone and tamoxifen in the 7,12-dimethylbenz(a)anthracene (DMBA) model starting treatment at week 7 after the induction of the tumour.

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2. Tibolone and the breast

Tibolone or its hydroxy metabolites do not contain an aromatic A-ring and it is therefore unlikely that they covalently bind to proteins or DNA. The effects of tibolone on the proliferation of breast cancer cells yielded inconclusive results. Tibolone was therefore investigated *in vivo* in the 7,12-dimethylbenz(a)anthracene (DMBA)-induced breast tumour rat model and in a nude mice model transplanted with normal breast tissue. The results with tibolone in comparison with tamoxifen in the DMBA model are presented in Fig. 1. Surprisingly, tibolone shows a similar effect to tamoxifen despite its lack of an anti-oestrogenic receptor activity and its inability to inhibit aromatase. The androgenic activity of tibolone does not seem to contribute to the positive effect in the DMBA model. Further investigations revealed that tibolone and its metabolites have an influence on intracellular steroid metabolising enzymes present in breast cancer cells. It was shown that sulphatase activity and 17β-hydroxysteroid dehydrogenase (type I) are inhibited and sulphotransferase activity is stimulated. Consequently, oestrogenic metabolites of tibolone, as well as endogenous oestrogens, are kept in an inactive, sulphated form and thus oestrogenic stimulation of the breast is prevented. In addition to the effect on the intracrine milieu, tibolone also influences cellular homeostasis. It inhibits cell proliferation of normal human breast epithelial cells and stimulates apoptosis. In this respect, tibolone behaves differently to oestrogens. Clinical studies have shown that tibolone users have significantly less breast pain and that their mammograms are not increased in density, in contrast to the findings observed in women using oestrogen–progestin combinations. Thus, tibolone clearly differs from oestrogens or oestrogen-progestin combinations on the breast in its effects on enzymes and cellular homeostasis.

Further reading

1. Kloosterboer HJ. Tibolone: a steroid with a tissue-specific mode of action. *J Steroid Biochem Mol Biol* 2001, **76**, 23 1–238.
2. Moore RA. Livial: a review of clinical studies. *Br J Obstet Gynaecol* 1999, **106**, 1–21.
3. Chetrite G, Kloosterboer HJ, Pasqualini JR. Effect of tibolone (Org OD14) and its metabolites on estrone sulphatase activity in MCF-7 and T-47D mammary cancer cells. *Anticancer Res* 1997, **17**, 135–140.
4. Gompel A, Kandouz M, Siromachkova M, *et al*. The effect of tibolone on proliferation, differentiation and apoptosis in normal breast cells. *Gynecol Endocrinol* 1997, **1**, 77–79.
5. Valdivia I Ortega D. Mammographic density in postmenopausal women treated with tibolone, estriol or conventional hormone replacement therapy. *Clin Drug Invest* 2000, **20**, 101–107.