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F. A. Helmond

LIVIAL AND ITS TISSUE SPECIFIC EFFECTS ON BREAST TISSUE

Summary

Conventional HRT consists of estrogens only or estrogens combined with progestogens. The exposure of breast tissue to these hormones results in well known side effects like increased breast pain and tenderness. Conventional HRT increases also mammographic density which results in a decreased sensitivity of routine mammographic screening. Tibolone is a tissue specific compound which reduces the uptake of estrogens from the circulation by breast tissue by means of inhibition of the sulphatase enzyme activity. This results in less breast pain and no increase in mammographic density when compared to conventional HRT.

INTRODUCTION

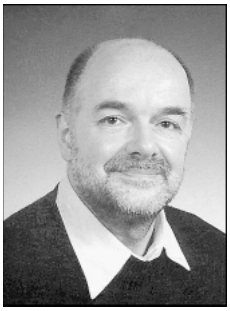
The active compound of Livial is tibolone, which is a tissue-specific steroid that has favourable effects on bone and climacteric symptoms in postmenopausal women, without estrogen-like stimulation of the endometrium or breast. After oral administration tibolone is rapidly converted by the enzymes 3α/β-hydroxysteroid dehydrogenases in the intestine and the liver into 3α- and 3β-OH metabolites. These hydroxymetabolites bind only to the estrogen receptor. In the circulation the most important metabolites are the biological inactive sulphated hydroxy-metabolites which can be activated again after desulphation by the enzyme sulphatase. Next to the hydroxy-metabolites the Δ4-isomer of tibolone can be detected for a short period in the circulation. This metabolite can be formed directly from tibolone or from the 3β-OH metabolite by the enzyme, 3β-hydroxysteroid dehydrogenase-isomerase [1]. This metabolite has a strong binding to the progesterone receptor and is responsible for tibolone's progestagenic activity. In addition it binds to the androgen receptor but not to the estrogen receptor. The estrogenic metabolites of tibolone in circulation may potentially stimulate the breast. The effects of tibolone on breast tissue have therefore been studied extensively.

THE MODE OF ACTION OF TIBOLONE ON BREAST TISSUE

Both, estrogens alone and estrogens in combination with a progestagen, stimulate the breast and epidemiological studies have shown that there is an increased risk for breast cancer with conventional HRT [2]. Preclinical studies have shown that the induction of breast tumours by DMBA can be inhibited by tibolone [3]. Studies in breast tissue with normal and cancer cells have provided evidence that tibolone and its metabolites inhibit cell proliferation and stimulate apoptosis (programmed cell death) by inhibiting expression of the apoptosis-regulating protein bcl-2 [4]. In addition, it has been shown that tibolone inhibits sulphatase activity [5] and diminishes therefore the formation of estrogenic compounds from their conjugated forms in breast tissue. Tibolone and its metabolites do not possess aromatase inhibiting activity or act as an anti-androgen. These studies show that sulphatase inhibition by tibolone and its metabolites prevent the breast from estrogenic stimulation. Based on these investigations it may be concluded that despite the presence of estrogenic metabolites in circulation tibolone shows a completely different effect on breast tissue than estrogens. This different effect of tibolone on breast tissue is confirmed in comparative clinical trials where it has been found that tibolone does not increase mammographic density and has a lower incidence of breast pain in comparison to conventional HRT. The effects of different types of HRT on mammographic density and breast pain will be discussed below.

BREAST DENSITY DURING TIBOLONE THERAPY

A number of studies have shown that conventional HRT treatment increases the density of non-fatty breast tissue and as a result can reduce the sensitivity of routine mammographic screening [6]. Evidence is also accumulating that the combination of estrogens and progestogens have a stronger effect on breast density than estrogens alone. Both the data of Lundström [7] and the results from the PEPI trial [8] point into that direction. In the latter study it has been found that the percentage of subjects with an increase in mammographic density is 0 % (placebo), 3.5 % (CEE only) and 23.5 % (CEE+MPA). Recently a study has been presented [9] in which the effects of placebo, tibolone and a continuous combined HRT preparation (2 mg E2 and 1 mg NETA; EN) on mammographic density have been investigated. In that double-blind study 166 subjects were equally randomised over the 3 groups and treated for 6 months. Density was assessed both as a percentage of the breast area with a dense pattern in classes of 20 % and by means of the Wolfe-score classification. It has been found that the proportion of subjects with an increase in breast density was 0 %, 5.9 % and 50 % in the placebo, tibolone and EN group respectively. The difference between tibolone and EN was highly significant ($p < 0.001$) and the difference between tibolone and placebo not ($p > 0.10$). The increase in Wolfe score showed virtually identical results. This study confirms and extends the findings in two earlier clinical studies with tibolone in which the breast density was ei-



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ther unaffected [10] or increased in only 1 out of 25 women [11].

Breast symptoms during tibolone therapy

Although breast enlargement and tenderness have been reported with tibolone, the incidence of these events is lower than with oestrogen-based HRT. For example, during long-term follow-up, 20 of 266 women (7.5 %) reported breast tenderness or enlargement. However, among 70 women who had switched from oestrogens to tibolone, only one (1.4 %) reported breast tenderness, whereas 14 (20 %) had experienced this problem with their previous oestrogen therapy [12]. Compared with continuous combined regimens, tibolone has produced fewer breast symptoms and lower discontinuation rates for breast-related problems. In a one year comparative randomized study of tibolone (N = 210) versus EN (N = 213), subjects were actively questioned about some possible side-effects like breast pain [13]. It has been found that the incidence of breast pain was statistically significantly ($p < 0.0001$) lower in the tibolone group (20 %) when compared to the EN group (54 %). In the previously mentioned study [9] the frequency of breast pain, reported as an adverse event (AE), was also significantly ($p < 0.001$) lower with tibolone (3.6 %) than with EN (33.3 %). In another one year comparative trial of tibolone (N = 250) versus 0.625 mg CEE continuously combined with 5 mg MPA (CM) (N = 251) in which subjects were randomized over the two groups [manuscript in preparation]. It has been found that the frequency of breast pain, reported as an AE, was significantly ($p < 0.001$) lower in the tibolone group (2 %) when compared to the CM group (17 %). Any breast tenderness with tibolone usually settles after the first 3 months of therapy [14]. Thus, the suppression of oestrogen production in the breast by tibolone translates into lower rates of breast symptoms in the clinical setting.

Conclusion

It can be concluded from both clinical and preclinical research that Livial does not stimulate breast tissue. Mammographic density is not increased during Livial treatment and the incidence of breast pain is significantly lower than with continuously combined HRT preparations.

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