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H. J. Kloosterboer, A. G. H. Ederveen

TIBOLONE – ITS TISSUE-SPECIFICITY AND BONE PRESERVING EFFECTS

Summary

Tibolone, the active compound of Livial®, causes tissue-specific effects in postmenopausal women preventing bone loss and climacteric complaints without stimulating the breast and the endometrium. Two 3-hydroxy metabolites with exclusive binding to the estradiol receptor (ER) and a Δ^4-isomer with binding to the progesterone and androgen receptor are found in circulation. In addition, a large amount of inactive sulfated hydroxy metabolites is found serving as a kind of reservoir of estrogenic activity, which can be achieved after the action of the enzyme sulfatase in bone. However, this does not occur in the breast and endometrium due to selective inhibition of this enzyme by tibolone and its metabolites. In the endometrium the estrogenic activity is also diminished by the local formation of the progestagenic metabolite. Tibolone is not aromatized by the enzyme aromatase.

In animal models tibolone has been proven to prevent bone loss due to inhibition of bone resorption. This occurs entirely via the ER pathway by binding of the two estrogenic hydroxy metabolites. Tibolone maintains both cortical and trabecular bone quality in mature rats.

Clinical studies in postmenopausal women have shown that tibolone induces a progressive increase in bone mineral density of the lumbar spine and femoral neck and a decrease of bone turnover as has been visualized by bone markers.

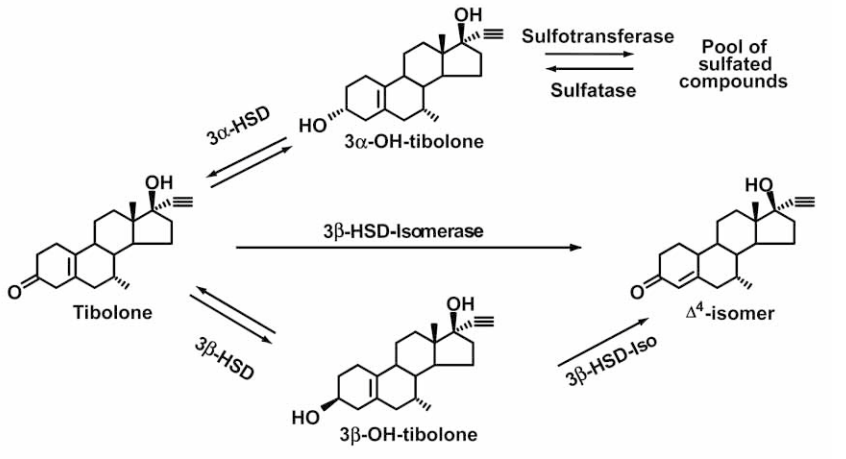
In conclusion, tibolone as a single compound shows unique properties being estrogenic on bone but not on the breast and the endometrium.

TIBOLONE'S METABOLISM AND TISSUE-SPECIFIC MODE OF ACTION

Tibolone is a compound with unique tissue-specific properties (for review see [1]). The clinical profile of tibolone, the active ingredient of Livial®, shows upon oral administration to postmenopausal women a very interesting tissue-specific effect. This profile was first shown in a study performed by Lindsay et al. [2]. In that study 2.5 mg of tibolone (Org OD14) prevented bone loss over two years and reduced the severity of menopausal complaints. In addition, it did not show evidence of endometrial hyperplasia. The compound expresses in bioassays estrogenic, progestagenic and androgenic properties, but the precise molecular basis for the observed clinical tissue-specificity remained obscure for some time. Later on, it appeared that these activities came from three different active metabolites as found in a kinetic study with labelled tibolone in postmenopausal women [3]. The proposed metabolism of tibolone is depicted in Figure 1. Tibolone with structural similarities to norethynodrel (3-keto group, Δ5-10 and 17α ethinyl) has an additional substituent at carbon 7 (7α methyl). The latter group has a clear influence on tibolone's metabolism and activity. After ingestion, tibolone is quickly metabolized in the liver and intestine by 3α hydroxysteroid dehydrogenase (HSD) and 3β HSD/isomerase forming the three active metabolites 3α and 3β hydroxy tibolone and Δ^4 tibolone.

The structurally related compound norethynodrel is primarily converted to norethisterone [4]. Apparently, this metabolic step seems to be diminished by the 7α methyl group in tibolone because the 3OH metabolites including the sulfates are the main metabolites in circulation. Recently, it was suggested that tibolone's estrogenic activity is due to conversion to 7α methyl ethinyl estradiol (7αMeEE$_2$) in the liver by the enzyme aromatase [5]. This observation is very surprising because the enzyme aromatase is lacking in adult human liver [6]. Furthermore, incubations of tibolone with human hepatocytes did not show any detectable aromatized product of tibolone [7]. Administration of labelled norethisterone [8] or norethynodrel [4] to man did neither result in any aromatized product.

Figure 1: Proposed metabolism of tibolone. Modified scheme from [1]. (HSD = hydroxysteroid dehydrogenase)



From the above-mentioned studies [4–8] it is considered very unlikely that 19-nortestosterone derived compounds with a 17α ethinyl group are converted to an aromatized product. For the conversion of testosterone to estradiol three hydroxylations at carbon atom 19 are catalyzed by the enzyme aromatase. Since this 19-methyl group is lacking in tibolone, norethisterone and norethynodrel it is hard to understand which mechanism may be responsible for such conversion. Nevertheless, Braselton et al. identified ethinyl estradiol by gas chromatography in a volunteer using a high dose of norethisterone [9]. Whether this finding is due to the used methodology requires further investigations. It is now well established that the estrogenicity of norethisterone is derived from non-aromatized metabolites [10]. This is also true for tibolone as metabolism [7] and receptor studies [11] have shown. The two 3-hydroxy metabolites of tibolone bind solely to the ER and not to androgen or progesterone receptor. The Δ^4-metabolite has affinity for the progestrone and androgen receptor. For the complete receptor profile of tibolone and its metabolites see Table 1. Besides the metabolism in the liver and intestine the metabolism in peripheral tissues can also have an impact on the final effect in a tissue. In human endometrial tissue, tibolone as well as 3β-hydroxy tibolone can be converted to the Δ^4-isomer, which has progestagenic activity [12]. The progestagenic activity may be even stronger than purely based on its receptor activity because the Δ^4-isomer is metabolically very stable due to the presence of the 7α methyl group. Another important regulatory mechanism in the tissue-specific effects of tibolone is the sulfation and desulfation of the OH-metabolites by the sulfotransferase-sulfatase system. This system is present in all tissues relevant to hormone replacement therapy (HRT) and especially plays a role in the breast and the endometrium. Chetrite et al. showed that tibolone and its metabolites could inhibit sulfatase activity in breast cells. As a consequence, metabolites of estradiol and the estrogenic metabolites of tibolone are kept in the inactive forms [13]. This leads to a lower stimulation of the breast compared to conventional HRT [14]. De Gooyer et al. showed that the inhibition of sulfatase occurs in a tissue-specific manner by tibolone and its metabolites [15]. In bone cells, no inhibition was found whereas strong inhibition was observed in breast cells and an intermediate effect was seen in endometrial cells. This means that sulfatase inhibition may contribute to the prevention of estrogenic stimulation in the endometrium in addition to the local formation of the progestagenic metabolite of tibolone [12]. Induction of sulfotransferase activity by the progestagenic metabolite may further contribute to diminish the estrogenic effect in this tissue. Clinically this leads to an atrophic endometrium in the majority of women [16]. The mode of action of tibolone on bone and its final effect on bone quantity and quality will be discussed below and compared to other bone remodeling compounds.

Tibolone and bone

Estrogens play an important role in bone remodeling as was demonstrated by deleting the genes for the estradiol receptors (ERs) in mice [17]. ERβ compensates for the deletion of ERα and the reverse is also true, but when both ERs are deleted a profound decrease in trabecular bone volume was observed. In rodents it was shown that the two estrogenic hydroxy metabolites of tibolone are responsible for the prevention of bone loss after ovariectomy. Tibolone prevents bone loss in both young [18] and mature rats [19] dose-dependently and to the same extent as seen with estrogens. The increase in bone markers, osteocalcin for bone turnover and urinary deoxypyridinoline/creatinine ratio for resorption, were also prevented. Besides estrogens both androgens and progestins have also positive effects on bone and the question raised whether the androgenic and progestagenic activity of tibolone may contribute to the final effect on bone. This has been studied with anti-hormones for the various steroid receptors [20]. The results of that study are depicted in Figure 2. The combination of tibolone with an anti-estrogen can prevent the maintenance of bone mass whereas the combinations of tibolone with an anti-androgen or anti-progestin have no effect. These results indicate that tibolone acts solely via the ER in this model. Tibolone prevents, like estrogens, deterioration of the skeleton at different bone sites and preserves trabecular and cortical bone strength in mature rats [19]. In contrast to tibolone, raloxifene, which has both agonistic and antagonistic activity for the ER, gives a lower bone protective effect than estrogens after a short treatment [21]. However, Turner et al. showed that after a longer treatment with raloxifene the effects on bone mass and bone strength were not different from estrogens [22]. In a monkey study designed to investigate the effects of tibolone in comparison to conjugated equine estrogens (CEE) and CEE plus medroxyprogesterone acetate (MPA) on coronary artery atherosclerosis the effects on bone were also evaluated [23]. The bone

Table 1: Steroid receptor binding profile of tibolone and its metabolites (ER = estrogen receptor; PR = progesterone receptor and AR = androgen receptor)

	ER	PR	AR
Tibolone	–	+	+
3α-OH-tibolone	+	–	–
3β-OH-tibolone	+	–	–
Δ^4-isomer	–	+	+

mineral density in the tibolone treated groups was higher than in the CEE and CEE+MPA treated groups.

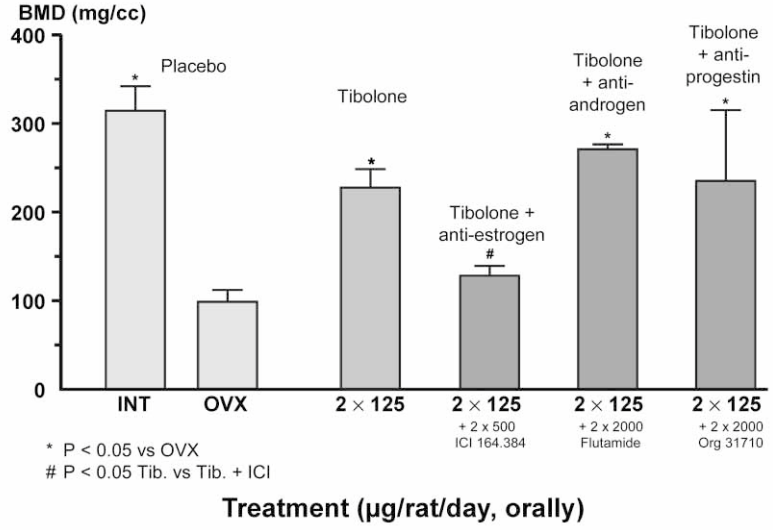
After the first double-blind clinical study with tibolone [2], two other studies confirmed the prevention of bone loss in early postmenopausal women [24, 25].

Tibolone appeared to be also efficacious on bone in elderly women [26]. A head to head comparison of tibolone with other anti-resorptive agents has never been made. A comparison from literature data can hardly be reliable because of differences in design, methodology and use of supplements. However, the results of one study with raloxifene [27] qualifies for a reliable comparison with the study performed by Gallagher et al. [25]. In Table 2 the effects of both compounds on the BMD in the lumbar spine and total hip are given. After two years of treatment tibolone appears to have a stronger effect than raloxifene on bone mineral density at both the spine and hip. The bone markers were also less decreased with raloxifene indicating that bone turnover is stronger influenced by tibolone. The effects of estrogens [28] on bone mass change from baseline were more or less comparable to that of tibolone in postmenopausal women. The slightly larger effect with estrogens may be due to the lack of use of calcium supplementation in the tibolone study. A study with the bisphosphonate alendronate in osteoporotic subjects showed a stronger effect, which is not surprising because of the use of a completely different population [29].

Table 2: Effects of tibolone (2.5 mg) and raloxifene (60 mg) on BMD increase (%) from baseline compared to placebo in postmenopausal women after 2 years treatment. Data from two randomized, double-blind, placebo-controlled studies [25, 27].

	Lumbar spine	Total hip
Tibolone [25]	5.2 %	4.5 %
Raloxifene [27]	2.4 %	2.4 %

Figure 2: Effects of tibolone alone and in combination with anti-hormones on bone mineral density in ovariectomized rats. (Adapted from Ederveen et al. [20])



Conclusion

Tibolone, the active ingredient of Livial®, displays tissue-specific effects via steroid receptor activation and enzyme regulation, leading to the prevention of bone loss and climacteric complaints in postmenopausal women without stimulating the breast and the endometrium. Tibolone acts on bone via the estradiol receptor and clinical data show similar effects on bone mineral density compared to estrogens.

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