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TIBOLONE AND THE ENDOMETRIUM – TIBOLONE AND BLEEDING

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INTRODUCTION

The main reason women abandon menopausal oestrogen therapy is the necessity for concurrent cyclical progestogen, which in turn results in cyclical withdrawal bleeding. Even with the so-called 'no bleed' continuous combined preparations of estrogen and progestogen, there is a much higher incidence of breakthrough bleeding than is generally appreciated. Also the side effects of some progestogens, particularly when taken continuously, are such that many women then discontinue therapy altogether.

These are thus the main reasons why at most some 10 % of women (at least in the United Kingdom) continue to take menopausal therapy for any length of time. Even in women with osteoporosis and other unequivocal indications for climacteric therapy, treatment is continued for an average for only four months. It is therefore clear that we have to provide more 'user friendly' menopausal therapy if the women who most need such treatment will continue to take it. This is where, in addition to established therapeutic benefits, tibolone comes into its own.

ENDOMETRIAL CHANGES IN WOMEN TREATED WITH TIBOLONE

Unlike estrogens, tibolone does not cause endometrial proliferation – indeed the endometrium atrophies. Histology of the endometrium showed poor stromal tissue and atrophied glands; in some specimens taken at curettage, only mucus could be found. After two years' tibolone, there was atrophic endometrium only in over 90 % of the specimens examined histologically; hyperplasia was never seen [1–3].

From the molecular point of view, tibolone is an analogue of norethynodrel but bears a closer structural resemblance to norethisterone. The absence of endometrial proliferation after tibolone is explained by the nature of the metabolites of the drug, and in particular by the specific enzymic conversion of tibolone which occurs in the endometrium. There are three main metabolites of tibolone, each with different affinities for estrogenic, progestogenic and and rogenic receptors – Δ^4 -isomer, 3α hydroxy metabolite and 3β hydroxy metabolite. It is the first of these, the Δ^4 -isomer, produced in the endometrium by a specific enzyme 3β hydroxy steroid dehydrogenase/isomerase [4], which is the important factor in the lack of endometrial proliferation after tibolone since it does not bind to estrogenic receptors. Hence there is no endometrial proliferation after tibolone and no necessity for concurrent progestogen administration to induce shedding of the endometrium with subsequent vaginal bleeding.

Tibolone itself binds, albeit weakly, to all three receptors – estrogenic, progestogenic and androgenic. The 3α and the 3β hydroxy metabolites bind weakly to estrogenic receptors but not to progestogenic or androgenic receptors.

Vaginal bleeding in women treated with tibolone

Despite the well documented absence, histologically, of stimulation of the endometrium by tibolone, it soon became apparent that vaginal bleeding occurred in clinical practice in women taking the drug, albeit intermittently and only occasionally. Our own experience is that vaginal bleeding in women taking tibolone is of the order of 12 % [5]. Rymer and colleagues [6] however reported an incidence of bleeding of 20 % [6] higher than we had found. In Rymer's study, the vaginal bleeding was most frequent in younger women – in those who had only recently entered on the menopause and in whom consequently endogenous estrogen was still significant. Since however we only gave tibolone to women after at least a years' amenorrhoea and more often to patients who had entered on the menopause some five or more years earlier, the average age of women for whom we have prescribed tibolone is much older than in those seen by Rymer and colleagues.

Cause of Vaginal Bleeding in Women Treated with Tibolone

We have now analysed the incidence and cause of vaginal bleeding in over 400 postmenopausal women started on tibolone during the years 1987–1996 [7], of whom 11 had previously undergone hysterectomy. OverTibolone And The Endometrium -Tibolone And Bleeding

> all these women had taken tibolone for a mean duration of close on three years $(35.2 \pm 1.3 \text{ months})$ – range 2–75 months). During this time 52 women reported vaginal bleeding whilst taking tibolone. In 43 women there was only one episode of bleeding; in eight there were two and in one three episodes of bleeding. Five women who had only recently discontinued estrogen therapy were lost to follow up. The remaining 47 were then investigated fully from the gynaecological point of view in an attempt to determine the precise cause of vaginal bleeding in each case.

The women who bled after tibolone in our series appeared to cluster into two groups – those who bled within four months of starting therapy ('early bleeders') and those who bled after more than a years' therapy ('late bleeders'). We have therefore analysed our findings both in the group of 47 women as a whole and then separately in the two groups as defined above – those who bled within four months of starting therapy and those who bled after more than a year.

Overall results

In the group as a whole, an intrauterine or cervical polyp was found responsible for vaginal bleeding in 11 women and uterine fibroids in seven. A thickened endometrium was observed on ultrasound in six women, in three of whom there was no histological abnormality; of the remaining three, two had benign simple hyperplasia whilst an early carcinoma *in situ* was found in the third woman. Carcinoma in situ was found in two women. In one of these, this was an incidental finding of abnormal cells in a specimen taken at dilatation and curettage performed in a woman with a bleeding cervical polyp. As a result of subsequent histological examination of the hysterectomy specimen, both the histologist and the surgeon who performed the hysterectomy concluded that bleeding in this woman had been from the cervical polyp and not from the region of the uterus with abnormal neoplastic cells. In the other woman, there had been a short episode of vaginal bleeding after which dilatation and curettage showed the presence of suspicious cells so hysterectomy was undertaken, revealing a carcinoma in situ.

Hysterectomy was performed in four of the 47 women who experienced vaginal bleeding whilst on tibolone – in two cases there was a carcinoma *in situ*, in one an endometrial polyp and intramural fibroadenomyosis and in the other simple endometrial hyperplasia.

Bleeding would seem to have been the result of the presence of significant levels of circulating estrogens in women who had only recently discontinued oestrogen therapy in 17 women. In a proportion of these however a discernible morphological cause for bleeding was also apparent.

Despite intensive investigation, no cause for vaginal bleeding could be found in 24 women, i.e. just over half the total investigated.

Early bleeders – 30 women

There was no difference in the mean age or duration of menopause as between early and late bleeders.

Although estrogen therapy was known to have been taken by more than half (17 women) of this group during the six months before switching to tibolone, an endometrial polyp was still found responsible for bleeding in two cases and fibroids in three. Even in the women who had taken estrogen shortly before staring on tibolone, an inactive endometrium was found on histology in 10 cases.

Late bleeders – 17 women

An endometrial polyp was responsible for the vaginal bleeding in five of the 17 women who bled after over a year's therapy. The numbers are too small to state whether there is any difference in the number of women who bled from a polyp after a years' tibolone therapy as compared with those who bled after less than four months' treatment.

As in the early bleeders, no apparent cause was found for the bleeding; also, the endometrium was inactive in half the 'late bleeders'.

37 of the original 47 women, including the two who were found to have carcinoma *in situ*, are still taking tibolone at the time of writing. In some cases this represents well over five years' therapy.

Thus although it is possible to relate the bleeding to estrogen

therapy in a proportion of those who bleed within four months of starting therapy and a discernible morphological cause such as a polyp was responsible in a significant proportion of cases, no obvious cause was found for vaginal bleeding in over half our patients. There was no endometrial thickening in such cases, only atrophy in specimens taken at hysteroscopy.

It must however be emphasised that vaginal bleeding in our women taking tibolone was never heavy and rarely lasted for more than a few days. Whilst discomfort or period-like pains might occur, irrespective of whether it was a bleed within four months' of starting therapy and thus possibly related to recent estrogen, or whether it was with a polyp, severe pain was not reported, only occasional 'period like' sensations. Although a thickened endometrium was apparent on ultrasound in five women overall, histological examination of endometrial tissue removed in their case showed a degree of benign hyperplasia in only two cases. In the other three an atrophic endometrium was observed.

INVESTIGATION OF WOMEN WHO BLEED ON TIBOLONE

Unless bleeding in a woman on tibolone is unequivocally related to very recent administration of estrogen or to elevated oestrogen concentrations in the blood, full investigation should be instigated in order to exclude a morphological cause. Our routine initial assessment is a pelvic ultrasound examination, preferably by the vaginal route. This may reveal a cause such as a polyp or fibroid formation. If endometrial thickening is seen in a woman who has not recently taken estrogens and who has been maintained for a year or more on tibolone, further investigation is mandatory. Endometrial thickening is *not* a normal consequence of tibolone therapy but suggests the possibility of some change either in hormonal balance or morphology. A vaginal smear should also be performed. Measurement of blood estradiol levels may be helpful in such cases.

In the light of the initial findings, further investigation may then be required – hysteroscopy which we performed in all doubtful cases but which did not necessarily reveal a cause although it was important to do so in a women with a thickened endometrium.

It is essential to exclude a morphological abnormality in a woman who bleeds in the course of tibolone therapy, unless it is within a very short period of her discontinuing oestrogen therapy. Even then, an ultrasound examination and a vaginal smear remain mandatory. In the overwhelming majority of cases it is our experience that bleeding does not recur and women may be reassured that they may continue on the drug. In any case, tibolone can be continued throughout the period of investigation, even in a woman where the cause is thought to be neoplastic. If any doubt exists however as to the nature of the possible cause, dilatation and curettage, preferably combined

with hysteroscopy, should be performed.

It is reassuring to all concerned that there is no need to discontinue tibolone whilst investigations are proceeding in order to determine the possible cause of bleeding. The majority of our patients who bled on tibolone and in whom either a discernible cause was found such as a polyp, fibroid formation or the two cases of carcinoma of the endometrium, and even those in whom no cause could be found, continued on tibolone during the period of investigation and thereafter. We are of course still following these women up in the long term.

Why bleeding occurs in a small percentage of women who take tibolone is not clear. We have already emphasised that in a younger woman, or those who have only recently discontinued estrogen, the circulating levels of estrogen may be sufficient to explain endometrial proliferation and even hyperplasia so that subsequent shedding of the endometrium occurs.

The suggestion has been made that there is increased uterine blood flow together with enhanced capillary fragility in women on tibolone. We ourselves, and others, have found a slight increase in maximal flow and a decrease in pulsatility index after tibolone but neither of these changes were significant and would thus not be sufficient to explain the bleeding, in particular since there is no evidence of endometrial hyperplasia – only inactive tissue. Capillary fragility of the uterine vessels is an unknown phenomenon.

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> It is also possible that vascular neogenesis occurs or that there is increased secretion and/or production of one or other of the vasoactive factors which may influence capillary growth and bleeding at local level. Whatever the answer, vaginal bleeding is by no means universal and is not sinister from the point of view of the long-term effects of the drug. Nevertheless, it is essential that it is investigated so as to exclude some other more sinister cause of bleeding, albeit unrelated to tibolone therapy as such.

FIBROID FORMATION AND TIBOLONE

Fibroid formation, as already indicated, was present in seven of our 47 women. There is however no evidence that increased fibroid formation or growth of pre-existing fibroids is increased in women who have been started on tibolone - rather the reverse. Indeed there are reports of a lack of stimulant effect on the growth of fibroids in women taking tibolone [8]. The demonstration of fibroids before starting tibolone is therefore not a contraindication to initiation of therapy with this drug.

The finding in two women of carcinoma *in situ* would not seem to be a worrying feature. It has not been possible to find accurate data on the incidence of carcinoma *in situ* of the endometrium overall in menopausal women and hence the number that one would expect in women treated with tibolone, if the drug had no adverse effect on the frequency in the incidence of this carcinoma. But from the available data both in our own series and those who have been giving the preparation long-term, there is no evidence, by contrast with effects of estrogen, of an increased incidence of carcinoma of the endometrium. A family history or preceding evidence suggestive of abnormal cells in a woman in whom surgery has not yet been performed is not a contraindication to the administration of tibolone.

SUMMARY

Tibolone (Livial), unlike estrogens, does not cause endometrial proliferation. The histological examination of the endometrium in specimens taken at curettage after two years' tibolone showed only atrophic endometrium in over 90 % of specimens examined; hyperplasia was never seen. The absence of endometrial proliferation after tibolone can be explained by the differential binding to estrogenic, progestogenic and androgenic receptors of its metabolites, the drug being metabolised in the endometrium by a specific enzymic process catalysed by 3ß hydroxysteroid dehydrogenase/ isomerase to the Δ^4 -isomer which does not bind to estrogenic receptors.

Nevertheless, in clinical practice there is an incidence of bleeding – of the order of 12 % – in postmenopausal women taking tibolone. In younger women, intermittent ovarian activity with secretion of estrogens may be responsible for this bleeding. At any age, a recent switch from postmenopausal estrogen therapy to tibolone may result in vaginal bleeding because of residual estrogen released from tissue depots.

Although a discernible morphological cause such as a polyp or fibroid was apparently responsible for the bleeding in a significant proportion, there was no apparent intrauterine cause found to account for vaginal bleeding in over half the 47 women out of some 500 patients on tibolone who bled in the course of treatment. A thickened endometrium was found in a few cases but with no pathological features on histological examination, and in the majority of those no morphological change, the endometrium was thin or atrophic. Bleeding was never heavy and was not accompanied by severe pain.

Bleeding after tibolone requires investigation. A morphological abnormality may be present even in women who have taken estrogens recently and experienced bleeding thereafter.

It is not however necessary to discontinue the drug whilst investigating vaginal bleeding. The majority of our patients continued happily without incident on tibolone during and after completion of investigations.

The incidence of carcinoma of the endometrium in the women who bled on tibolone does not seem to be more than would be expected in postmenopausal women. Even when carcinoma of the endometrium has been found, and hysterectomy performed, tibolone may safely be continued.

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