Effects of tibolone on serum concentrations of lipoprotein(a) in postmenopausal women

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Objective: To evaluate the effects of tibolone (Org OD14), a synthetic steroid used for the relief of postmenopausal symptoms, on serum concentrations of lipoprotein(a) (Lp(a)), an independent risk marker for coronary heart disease. Design: Subset of women participating in a non-randomized prospective trial of tibolone therapy. Twenty-seven women requesting relief of menopausal symptoms were treated with tibolone 2.5 mg/day for six months; 27 women who did not request treatment acted as controls. Results: Tibolone induced a substantial fall (p < 0.001) in serum Lp(a) levels (median change −48%, range −100% to +3%). Conclusions: In terms of cardiovascular risk, the ability of tibolone to lower serum concentrations of Lp(a) may be advantageous in view of the unwanted reduction in high density lipoprotein concentrations which has previously been demonstrated in users of this steroid.

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Postmenopausal oestrogen replacement therapy reduces the incidence of coronary heart disease (CHD) by 50% (1). Although mechanisms such as effects on arterial blood flow (2) are likely to be involved, this protection may be at least partially explained by the theoretically favourable serum lipoprotein profile seen in women taking postmenopausal oestrogen (3). These women have reduced serum concentrations of low density lipoproteins (LDL), lipoproteins thought to increase CHD risk, together with increased concentrations of the protective high density lipoproteins (HDL) fraction.

Tibolone [(7α, 17α)-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one; “Jivial” (Organon BV)] is a synthetic steroid with weakly oestrogenic, progestagenic and androgenic properties which relieves postmenopausal symptoms and may prevent osteoporosis (4). Unlike postmenopausal oestrogen, tibolone does not stimulate the endometrium and so obviates the need for monthly progestagen-induced menstrual bleeds in non-hysterectomized women. However, tibolone reduces serum HDL concentrations by up to 30% (5–7), whereas an ideal therapy would match the increases in HDL seen with postmenopausal oestrogens (8). Although there are no controlled trials of the effects of lowering HDL on CHD incidence, evidence for the long-term significance of this lipoprotein is increasing (9, 10).

Serum lipoprotein(a) (Lp(a)) may provide a link between lipid metabolism, coagulation and fibrinolysis in the pathogenesis of CHD (11). Lp(a) is a cholesterol-rich lipoprotein which resembles LDL but is present only in trace amounts in most individuals (12, 13). Those with elevated (> 300 mg/l) serum Lp(a) concentrations are at high risk of CHD, regardless of their serum cholesterol concentration (14, 15).

Because androgenic steroid hormones are able to lower serum Lp(a) concentrations (16), we wondered whether tibolone, a weakly androgenic steroid (17), would share this property.

Subjects and method

Subjects

The study group comprised 54 postmenopausal women participating in a larger non-randomized trial of the clinical and metabolic effects of tibolone. Volunteers had been offered a choice of tibolone therapy or no therapy. All women had undergone a natural menopause between 3 and 36 months prior to the study and had elevated gonadotropin concentrations consistent with ovarian failure. None was obese (ideal body weight <120% by Metropolitan Life Tables) and none had been previously exposed to any form of hormone replacement therapy. None was taking any medication known to affect lipid metabolism. Full informed consent was obtained in each case and the study was approved by the local ethics committee.

Non-fasted blood samples were taken prior to the study and after six months of tibolone therapy (2.5 mg/day) or six months of no therapy in the case of controls.
Table 1. Serum lipids and lipoprotein concentrations in women treated with tibolone and controls.

<table>
<thead>
<tr>
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<th>Tibolone-treated group (N = 27)</th>
<th>Control group (N = 27)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline (6 months)</td>
<td>Baseline (6 months)</td>
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<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.5 (1.2)</td>
<td>6.3 (1.0)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.1 (0.4–3.3)</td>
<td>1.5 (0.7–5.2)†</td>
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<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.4 (0.2)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>Lp(a) (mg/l)</td>
<td>146 (0–932)</td>
<td>36 (0–719)</td>
</tr>
</tbody>
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‡ Mean values with sd in parentheses; § median values with range in parentheses.
* p < 0.05, ** p < 0.01; significant differences between change in tibolone group over six months and change in control group (Mann–Whitney U test).
† p < 0.05; significant difference between control and tibolone group at baseline (Mann–Whitney U test).
Abbreviations: HDL, high density lipoproteins; Lp(a), lipoprotein(a).

Laboratory methods

Serum concentrations of total cholesterol and triglycerides were measured using fully enzymatic assays. HDL cholesterol concentrations were measured following precipitation of other lipoproteins with phosphotungstic acid and magnesium ions (18). Because the Friedewald formula (19) is invalid for non-fasting samples, we were unable to obtain estimates of LDL cholesterol in these women.

Serum Lp(a) concentrations were determined in contingency samples (stored at −20°C) from 27 women treated with tibolone and 27 controls. Lp(a) was measured using an ELISA method (Biopool AB, Umeå, Sweden). Within-batch and between-batch coefficients of variation for this assay were 4 and 7%, respectively.

The laboratory was blinded to the origin (tibolone or control) of these samples.

Statistical analyses

Differences between the groups at baseline were compared using Student’s t-test (unpaired), except in the cases of serum triglyceride and Lp(a), where the data were not normally distributed and so the Mann–Whitney U test was used. Changes from baseline in lipids and lipoproteins in tibolone-treated women and in controls were compared using the Mann–Whitney U test. Spearman correlations coefficients were derived to investigate relationships between changes in lipids and lipoproteins.

Results

At baseline, the mean age in the tibolone group was 51.1 (sd 4.2) years vs 53.3 (sd 3.6) years for controls; the mean body weight in the two groups was 65.3 (sd 8.9) kg and 69.0 (sd 12.4) kg, respectively. These differences were not statistically significant. There were no significant changes in body weight during the six-month study period. At baseline, women in the tibolone group had slightly lower (p = 0.048) serum triglyceride concentrations than did controls (Table 1). These women also had higher Lp(a) levels at baseline than did controls, although this was not statistically significant (p = 0.12, Mann–Whitney U test).

There were no significant changes in serum lipids or lipoproteins in the control subjects. In women treated with tibolone, serum total cholesterol concentrations fell by a median 9% (range −34% to +8%); HDL cholesterol concentrations fell by 27% (−50% to 0%), and triglyceride concentrations fell by 22% (−71% to +46%) (Table 1). Striking falls in serum Lp(a) concentrations (median fall 48%, range −100% to +3%) were seen in response to tibolone (Table 1, Fig. 1). These changes in Lp(a) did not correlate significantly with the changes in total cholesterol (r = −0.12), HDL cholesterol (r = 0.15) or triglycerides (r = 0.25).

Discussion

Tibolone reduced serum concentrations of total cholesterol, triglycerides and HDL cholesterol, in agreement with the findings of others (5–7, 20, 21). According to current concepts, these effects on total cholesterol and triglycerides would decrease CHD risk, whereas the effect on HDL would increase risk. Our finding of a potentially
beneficial effect on Lp(a) may help restore the balance of risk associated with tibolone therapy.

Although Kloosterboer et al. (7) have proposed that the effect of tibolone on HDL concentrations is transient, we consider this possibility unlikely. The earliest metabolic study of tibolone (5) showed a 30% fall in HDL cholesterol concentrations after six weeks, a change considered by the authors to be due to the androgenicity of the steroid. A similar placebo-controlled study (6) confirmed this reduction and showed that it was maintained for at least 12 weeks. Farish et al. (20) compared 24 women treated with tibolone for five years with a mixed group constructed from 18 women who had taken placebo for five years and six untreated women. No baseline data were presented. HDL cholesterol concentrations were 12% lower in the tibolone group, although this was not statistically significant. A similar non-significant reduction in HDL was seen in 27 women treated with tibolone for six months (21).

In the studied of 14 women reported by Kloosterboer et al. (7), HDL cholesterol concentrations fell by a third after one year, but normalized after a further two years' therapy. Such reversion of lipoprotein changes in response to steroid hormones is unusual. Methodological drift could not be excluded, as there was no control or comparison group and no information was provided on assay performance over the three years. The changes reported for HDL cholesterol conflicted with changes seen in HDL phospholipids and apolipoprotein A1. These fell by 18% and 23%, respectively, after one year, paralleling the fall in HDL cholesterol. However, their concentrations remained low over the subsequent two years of the study. These two markers of HDL may provide a better measure of HDL concentration than does HDL cholesterol, as they account for over half the HDL mass, more than double the contribution from cholesterol (22).

Long-term studies of hormone replacement therapy which do not run a concurrent control or reference group have been criticized (23). Until such studies are performed the well-documented effect of tibolone on HDL concentrations should remain a factor in assessing the risk/benefit ratio of such therapy.

Preliminary evidence indicates that the menopause increases serum Lp(a) concentrations (24). The ability of postmenopausal hormone replacement therapy to reverse this increase was first suggested by the data of Soma et al. (25). These authors demonstrated falls in serum Lp(a) concentrations in 10 women treated with conjugated equine oestrogens (1.25 mg/day) plus medroxyprogesterone acetate (10 mg/day for 10 days per cycle) for one year. However, Muesing et al. (26) were unable to obtain such a reduction.

The ability of tibolone to reduce serum Lp(a) concentrations resembles that of other testosterone derivatives, such as norethisterone (27), stanzolol (28) and danazol (29). These are among the largest changes reported for Lp(a), a lipoprotein remarkably resistant to drug treatment or other factors (12). Serum Lp(a) concentrations vary inversely with the molecular weight of the isofoms of apo(a), the distinctive glycoprotein of Lp(a) (30). In our previous study (29) we have shown that steroid-induced falls in Lp(a) concentration involve changes in Lp(a) concentration, not in Lp(a) isoform pattern.

The mechanisms by which testosterone derivatives affect Lp(a) are unknown. Apolipoprotein(a), the specific protein component of Lp(a), is a giant mutant of plasminogen (31) and we have proposed (29) that the effect of these steroids on Lp(a) may be related to changes in plasminogen metabolism. The ability of tibolone to increase plasminogen concentrations (6) would be consistent with this hypothesis.

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