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Tibolone Improves Myocardial Perfusion in Postmenopausal Women With Ischemic Heart Disease

An Open-Label Exploratory Pilot Study

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OBJECTIVES We sought to determine the effect of tibolone on myocardial perfusion in postmenopausal women with ischemic heart disease.

BACKGROUND Tibolone is a steroid that relieves climacteric symptoms and prevents osteoporosis. Recent studies have suggested a cardioprotective effect of this compound. However, its role on myocardial perfusion remains uncertain.

METHODS Single-photon emission computed tomography myocardial perfusion imaging was performed in 26 postmenopausal women. Patients were randomly assigned to tibolone for six months (treatment group) or to usual care (control group). All women underwent cardiac imaging at baseline and at six months.

RESULTS Mean stress perfusion defect (summed stress score) was moderate and did not differ between the two groups (8 ± 3 vs. 9 ± 4; $p = NS$). Summed difference score also was similar for both groups (7 ± 3 vs. 8 ± 3; $p = NS$). The six-month study reveled that summed stress and summed difference scores significantly improved in the treatment group (to 3 ± 3 and to 2 ± 2; $p < 0.001$) whereas it remained unchanged for control patients (to 10 ± 4 and to 8 ± 2; $p = NS$).

CONCLUSIONS In postmenopausal women with ischemic heart disease, six months of therapy with tibolone significantly improved stress myocardial perfusion and the "amount of ischemia." (J Am Coll Cardiol 2006;47:559–64) © 2006 by the American College of Cardiology Foundation

Specific-activity steroids have the beneficial effects of estrogen on bone and brain without the known increased risk for breast cancer and endometrial hyperplasia observed in long-term users of estrogen. Tibolone, a specific-activity steroid, is a synthetic compound that relieves climacteric symptoms and prevents osteoporosis (1).

Recent studies have reported that tibolone therapy might be of benefit in the prevention of cardiovascular disease. In healthy postmenopausal women, tibolone tends toward increased fibrinolysis and improves endothelial function (2,3). Interestingly, in women with coronary artery disease (CAD), it has been suggested that tibolone might attenuate the ischemic burden (4). However, its role in modulating myocardial perfusion remains uncertain. In this open-label pilot study, the objective was therefore to evaluate the effects of tibolone on myocardial perfusion in postmenopausal women with ischemic heart disease (IHD) as assessed by single-photon emission computed tomography (SPECT).

METHODS

Study population and design. Twenty-six postmenopausal women not on hormone-replacement therapy referred for a clinically indicated SPECT myocardial perfusion study with stress-induced perfusion defects were enrolled. All had cessation of menses of one year or longer, a normal mammogram, breast and pelvic examinations, and pap test within six months of the study. Patients with recent history of myocardial infarction (<1 month), severe aortic stenosis (as assessed by echocardiography), known or suspected cancer, or undiagnosed abnormal vaginal bleeding were excluded.

This study is a prospective randomized open-label study. Randomization was performed using a table with random numbers. After their baseline SPECT scans, all patients were assigned randomly to usual care (control group) or to tibolone (Paraclim, ELEA Pharmaceuticals, Buenos Aires, Argentina) at 1.25 mg/day for six months (treatment group). Vaginal ultrasound was performed on the subjects the day before they started tibolone therapy and then at six months. All women underwent SPECT imaging at baseline and at six months. Beta-blockers and calcium antagonists were stopped four days before each scan and caffeine 24 h before the test in all patients.

Patients performed a symptom-limited exercise stress test on both sessions. Dipyridamole was infused in one patient of each group (because of poor exercise tolerance in one and the development of left bundle brunch block at peak exercise in the other patient). In all but one patient (because of a physical inability to exercise) the stress testing modality was maintained for the second SPECT scan. Rate-pressure product (RPP) was calculated in the patients that underwent exercise stress testing.

Coronary angiography was performed within 6 ± 4 months of the baseline scan. Significant CAD was defined as ≥50% diameter narrowing of a major coronary artery or

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Abbreviations and Acronyms

CAD = coronary artery disease
IHD = ischemic heart disease
NO = nitric oxide
RPP = rate-pressure product
SDS = summed difference score
SPECT = single-photon emission computed tomography
SRS = summed rest score
SSS = summed stress score

one of its major branches on visual analysis. The study was approved by the Research Subjects Review Board and the informed consent was performed for each woman.

Single-photon emission computed tomography perfusion imaging and image analysis. Myocardial perfusion imaging was performed using previously described same-day stress-rest protocol. At peak exercise, 8 to 10 mCi of ^{99m}technetium-sestamibi were injected and 25 to 35 mCi for resting images. In the two patients that underwent dipyridamole-hyperemia, 0.56 mg/kg were infused over the course of 4 min. The acquisition SPECT was performed using a dual-head gamma camera over a 180° elliptical orbit. Data were acquired in a 64 × 64 matrix for 60 projections in a step and shoot format.

Consensus interpretation for myocardial perfusion data with visual over-reading by three readers was performed. Unblinded semiquantitative analysis was accomplished using the Cedars method (5). A summed stress score (SSS), reflecting quantitative defect extent and severity, a summed rest score (SRS), and a summed difference score (SDS), reflecting "amount of ischemia" were calculated. Differences in summed perfusion scores from baseline to six-month perfusion study were rated as previously reported (>3 = "improved," >−3 to <3 = "no change," <−3 = "worse") (6). Resting images were gated and data were processed with QGS software (Cedars QGSTM program, Los Angeles, California) (7).

To address a scan interpretation bias, we also performed an automated quantitative analysis of the perfusion images using the CEqual software (Atlanta, Georgia) in all participants (8).

Statistical analysis. Continuous measures are expressed as mean values ± SD. Dichotomous variables are presented as a number or percentages. Comparisons within groups (at baseline and at six months) were performed using the paired Student *t* test for continuous variables and Wilcoxon signed rank test for ordinal variables. Comparisons between groups were performed using the Fisher exact test. Continuous variables were compared by unpaired Student *t* test. Ordinal variables were analyzed by Mann-Whitney rank sum test. Statistical significance was accepted at a level of $p < 0.05$.

RESULTS

Study subjects. After randomization, 11 women were enrolled in the treatment group and 15 in the control group.

Table 1. Baseline Characteristics of the 21 Postmenopausal Women Completing the Study Protocol

	Treatment Group (n = 10)	Control Group (n = 11)
Age, yrs	63 ± 11	67 ± 7
Duration of menopause, yrs	17 ± 11	21 ± 9
Body mass index, kg/m^2	27.39 ± 3.29	26.66 ± 3.72
Hypertension, n	8 (80%)	8 (73%)
Diabetes, n	2 (20%)	3 (27%)
Hypercholesterolemia, n	3 (30%)	4 (36%)
Cigarette smoking, n	1 (10%)	0
Family history of CAD, n	6 (60%)	6 (55%)
Previous myocardial infarction, n	3 (30%)	4 (36%)
Previous coronary bypass surgery, n	0	1 (9%)
Previous percutaneous coronary intervention, n	2 (20%)	2 (18%)
Coronary angiography, n	7	9
1 = vessel disease	3 (42%)	3 (33%)
2 = vessel disease	2 (29%)	3 (33%)
3 = vessel disease	2 (29%)	3 (33%)
Indications for SPECT imaging		
Chest pain or dyspnea, n	8 (80%)	9 (82%)
Asymptomatic with known CAD, n	2 (20%)	2 (18%)

All p = NS between groups.
CAD = coronary artery disease; SPECT = single-photon emission computed tomography.

One patient under tibolone was excluded because of vaginal bleeding. Thus, 10 patients comprised the treatment group. None of the women exhibited endometrial hyperplasia after tibolone treatment. Four women in the control group were excluded before the second scan (because of coronary revascularization in two and failure of subsequent follow-up in the other two participants). Thus, 11 women comprised the control group. Table 1 shows the baseline characteristics of the 21 women completing the study. Coronary angiography was obtained in 16 participants. Significant CAD was found in all patients. Two women in each group underwent SPECT imaging for diagnosis of CAD. Table 2 shows concomitant medications taken at baseline. They were not different at six months for both groups. None of the 21 patients were revascularized before the second scan.

Stress testing. In the treatment group, five patients exhibited chest pain and two exhibited ST-segment depression during stress. At six months, four women exhibited chest pain and one showed ST-segment depression during stress.

Table 2. Concomitant Medication Taken at Baseline

	Treatment Group	Control Group
Aspirin	10	9
Beta-blockers	6	8
Nitrates	3	3
ACE inhibitors	3	5
Calcium channel blockers	6*	0
Statins	3	3
Insulin	0	1
Sulfonylureas	1	0

*p = 0.011 vs. control patients.
ACE = angiotensin-converting enzyme.