Increased Cholesterol Levels During Paroxetine Administration in Healthy Men

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Background: Despite the frequent use of selective serotonin reuptake inhibitors in patients with coronary heart disease (CHD), their effects on plasma lipid levels have not been systematically investigated. Our objective was to assess the effects of 8 weeks of paroxetine administration on plasma cholesterol and triglyceride levels.

Method: Blood samples were collected at baseline, after 8 weeks of paroxetine administration, and post-discontinuation in 18 healthy male volunteers.

Results: In the 16 of 18 patients whose plasma levels of paroxetine indicated an unequivocal compliance to treatment, paroxetine administration induced an 11.5% increase in low-density lipoprotein cholesterol (LDL-C), which normalized after paroxetine discontinuation.

Conclusion: The magnitude of the paroxetine-induced increase in LDL-C would lead to a minor increase in CHD risk in a minority of healthy male volunteers without associated CHD risk factors but might increase LDL-C sufficiently to warrant therapeutic intervention in patients with established CHD, based on the National Cholesterol Education Program guidelines.

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The association between major depressive disorder (MDD), and to a lesser extent anxiety disorders, and coronary heart disease (CHD) has been well established.[1,2] Nearly a quarter of patients suffering from CHD will be affected by MDD. Major depressive disorder is an independent risk factor for cardiovascular events and mortality not only in patients with established CHD,[3–5] but also in individuals initially free of cardiovascular pathology.[6] High anxiety levels in post–myocardial infarction patients have also been associated with increased risk of cardiovascular complications.[7] In addition, physically healthy subjects with high levels of phobic anxiety, a characteristic of panic disorder, have been shown to present an increased risk of sudden cardiac death.[8] Selective serotonin reuptake inhibitors (SSRIs) are the first-line treatment for MDD and most anxiety disorders,[9] particularly panic disorder. The most recent clinical guidelines for MDD and anxiety disorders treatment recommend SSRI administration for at least 1 year to avoid relapses. A lifetime treatment is also recommended after the occurrence of 2 or more depressive episodes.[10]

Considering the high percentage of patients suffering from CHD and comorbid MDD and/or anxiety disorders as well as the high frequency of SSRI prescriptions, it is surprising that the effects of SSRIs on plasma cholesterol (an easily measurable and well-established cardiovascular risk factor) have never been systematically investigated. As a result of postmarketing reports, a potential association between cholesterol level increase and SSRI treatment is now indicated in medical compendiums as a possible rare occurrence. However, the causal relationship cannot be ascertained due to the multiple confounding factors associated with postmarketing reports.

Panic disorder affects 1% to 5% of the overall population[11] and is characterized by recurrent panic attacks, which consist of sudden episodes of intense fear associated with several cognitive and somatic symptoms such as dyspnea, palpitations, chest pain, and diaphoresis.[12] Increased cholesterol levels have been shown in panic disorder patients and have been correlated with the frequency and intensity of panic attacks in patients with panic disorder.[13] Logically, we hypothesized that effective antipanic therapy with SSRIs will decrease cholesterol levels in panic disorder patients. Contrary to our hypothesis, we

found that successful treatment with SSRIs (primarily sertraline and paroxetine) was associated with a statistically and clinically significant increase in low-density lipoprotein cholesterol (LDL-C) in a prospective but naturalistic study of panic disorder patients.[14] Due to the methodological limitations of this pilot study, we decided to systematically and prospectively test the effects of paroxetine on plasma cholesterol levels in healthy male volunteers, controlling for multiple potential confounding variables such as weight, diet, and smoking. By choosing to perform the study in healthy male volunteers, we intended to avoid the potentially confounding effects of paroxetine-induced remission of psychopathology on cholesterol levels. For instance, successful antidepressant treatment of a depressive episode will normalize symptoms such as decreased appetite, an effect that could alter cholesterol levels independently of the antidepressant's pharmacodynamic action.

We hypothesized that LDL-C levels would be increased compared to baseline following an 8-week treatment period with paroxetine and would normalize after paroxetine discontinuation.

METHOD

Subjects

Eighteen male (mean ± SEM age = 24.89 ± 1.26 years) nonsmokers participated in the study. All subjects were medication free and had no clinical or biological medical evidence of cardiovascular disease or other medical conditions at the time of the study, as indicated by normal findings upon physical examination, electrocardiogram, plasma thyroid-stimulating hormone, and complete blood count. The Structured Clinical Interview for DSM-IV Axis I Disorders[12] was used to exclude any Axis I psychiatric disorder. Subjects gave their informed consent after the procedure and possible side effects were fully explained.

Experimental Design

Paroxetine was initiated at a dose of 10 mg/day for 3 days and then increased to 20 mg/day for 8 weeks. Prior to discontinuation, the paroxetine dose was reduced to 10 mg/day for 5 days and then stopped.

General Procedures

Fasting (> 12 hours) serum concentrations of total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides were obtained at baseline, after 8 weeks of paroxetine administration, and 5 days after paroxetine discontinuation. The cholesterol assays employed enzymatic reactions and colorimetry. The accuracy and precision of the cholesterol and triglyceride assays satisfied the specifications of the National Cholesterol Education Program (NCEP).[15]

Weight and dietary alcohol and fat intake were assessed at baseline and at 8 weeks of paroxetine treatment. Assessment of diet was performed by a semiquantitative food frequency questionnaire.[16] Changes in physical activity were assessed at baseline, after 8 weeks of paroxetine administration, and post-discontinuation by a 7-day recall interview.[17] Plasma paroxetine levels were obtained on the last day of the eighth week of paroxetine administration. On the day of blood collection for measurement of paroxetine levels, subjects were instructed to take their dose of paroxetine at home, 3 hours prior to scheduled blood sampling. Plasma paroxetine levels were analyzed by gas chromatography with electron-capture detection.[18] The purpose of this measurement was to assess compliance of the subjects to paroxetine administration. As a result, 2 subjects were excluded from the analysis because of lack of detection of satisfactory plasma paroxetine levels, suggesting poor medication compliance. Female subjects were excluded since cholesterol levels fluctuate during the menstrual cycle.[19]

Statistical Analysis

Repeated measurements analysis of variance, with time as the within-subjects variable, was applied to measurements of lipids and physical activity. Post hoc analysis was performed using a 2-tailed paired t test analysis where appropriate. Changes in weight and diet were examined by a 2-tailed paired t test. A p value less than 5% was considered significant. All statistical analyses were conducted using SPSS statistical software for Windows (SPSS Inc., Chicago, Ill).

RESULTS

Based on the analysis of the data obtained for the 16 subjects for whom plasma levels of paroxetine indicated satisfactory medication compliance, a main time effect was found for total-cholesterol and LDL-C levels but not for HDL-C or for triglyceride levels (Table 1). LDL-C levels increased by 11.5% after 8 weeks of paroxetine administration compared to baseline and normalized after paroxetine discontinuation. In 3 (19%) of the 16 subjects, the post-paroxetine treatment serum LDL-C levels were greater than 2.59 mmol/L (100 mg/dL). No significant changes in physical activity, weight, or diet were detected. The results remained significant, although to a lesser degree, when the 2 subjects in whom compliance to paroxetine administration was doubtful were included in the analysis.

DISCUSSION

We found that paroxetine administration in healthy male volunteers induces an 11.5% mean increase in LDL-C that normalizes after discontinuation. This nor-

Table 1. Summary of Results for 16 Healthy Male Volunteers Treated With Paroxetine

Variable	Baseline[a]	Paroxetine[a] (8 weeks)	Post-Discontinuation[a]	Time Effect			Analysis[b]		
				Statistic	df	p	Statistic	df	p
LDL-C levels				F = 6.86	2,14	.004	t = 2.24*	15	.04
(mmol/L)	2.08 ± 0.59	2.31 ± 0.55	1.97 ± 0.56				t = 3.87†	15	.001
(mg/dL)	80.50 ± 22.83	89.4 ± 21.30	76.20 ± 21.70						
Total-C levels				F = 3.93	2,14	.05	t = 1.39*	15	.18
(mmol/L)	3.78 ± 0.69	4.01 ± 0.78	3.65 ± 0.74				t = 2.96†	15	.01
(mg/dL)	146.29 ± 26.70	155.20 ± 30.20	141.30 ± 28.70						
HDL-C levels				F = 0.49	2,14	.56	N/A		
(mmol/L)	1.19 ± 0.35	1.24 ± 0.42	1.21 ± 0.40						
(mg/dL)	46.05 ± 13.50	48.00 ± 16.20	46.80 ± 15.50						
Triglyceride levels									
(mmol/L)	1.14 ± 0.60	1.08 ± 0.89	1.01 ± 0.70	F = 0.28	2,14	.75	N/A		
(mg/dL)	44.10 ± 23.20	41.80 ± 34.40	39.10 ± 27.10						
Polyunsaturated fat daily intake (g)	15.30 ± 7.00	19.16 ± 19.50	N/A	t = 0.97	15	.35	N/A		
Saturated fat daily intake (g)	31.30 ± 16.48	32.57 ± 16.41	N/A	t = 0.66	15	.52	N/A		
Alcohol daily intake (g)	0.23 ± 0.24	0.21 ± 0.26	N/A	t = 0.17	15	.87	N/A		
Weight (kg)	79.6 ± 17.89	78.3 ± 16.04	N/A	t = 1.71	12	.11	N/A		

[a]Values represent mean ± SD. Significant value $p < .05$.
[b]Two-tailed paired t test post-hoc.
*Paroxetine (8 weeks) compared with baseline.
†Paroxetine (8 weeks) compared with post-discontinuation.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, total-C = total cholesterol, N/A = not applicable.

malization of LDL-C, in association with the control for multiple potential confounding factors and absence of psychopathology, suggests a causality link between paroxetine administration and the increase in LDL-C. The timing of our plasma sampling for paroxetine levels (only 3 hours post-paroxetine intake, i.e., during the absorption phase) prevented us from performing meaningful correlations between LDL-C and paroxetine levels, but allowed the detection of possible poor medication compliance in 2 subjects.

According to the third report of the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment Panel III), LDL-C is the primary factor in predicting CHD risk.[15] Several population studies including the Framingham Heart Study,[20] the Multiple Risk Factor Intervention Trial,[21] and the Lipid Research Clinics trial,[22,23] found a direct relationship between levels of LDL cholesterol (or total cholesterol) and the rate of new onset of CHD in men and women initially free of CHD. Other studies in clinical populations have shown the same relationship for recurrent coronary events in patients with established CHD.[24,25] The latest NCEP guidelines indicate that any LDL-C above 100 mg/dL (2.59 mmol/L) is atherogenic, even in healthy subjects.[15] Epidemiologic data show a continuous log-linear relationship between serum cholesterol levels and CHD risk.[15] Therefore, any increase in LDL-C above 100 mg/dL carries an associated increase in CHD risk. However, the negative prognostic value (percentage of a cardiovascular event at 10 years, for example) of such an increase is greater in the presence of an established CHD or diabetes or 2 or more associated CHD risk factors (hypertension, smoking, family history of premature CHD).[15] Healthy subjects without CHD risk factors (such as those selected in our study) with a paroxetine-induced increase in LDL-C above 100 mg/dL would most likely experience a minor increase in CHD risk. However, current NCEP guidelines do not deem this risk (increase in serum LDL-C levels in healthy subjects without CHD risk factors) high enough to intervene if the LDL-C levels are below 160 mg/dL (4.13 mmol/L).[15]

In our study, 3 of 16 subjects displayed a paroxetine-induced increase in LDL-C above 100 mg/dL but below 160 mg/dL. We can therefore conclude that, for 19% of the healthy subjects without associated CHD risks that we studied, the observed paroxetine-induced increase in LDL-C, if persistent, would lead to an increased CHD risk that would not commend therapeutic intervention. On the contrary, the same paroxetine-induced increase in LDL-C above 100 mg/dL (2.58 mmol/L) in subjects with established CHD (a frequent occurrence in patients suffering from MDD or anxiety disorder who need to be treated with SSRIs such as paroxetine) would require therapeutic intervention under the NCEP guidelines.

The pharmacodynamic mechanism underlying the increase in LDL-C remains unclear, but appears to be shared at least by paroxetine, sertraline, and venlafaxine.[26] Indeed, our initial pilot study showed SSRI-induced increases in LDL-C levels in panic disorder patients, most of whom were treated with sertraline.[14] Our findings, in combination with recent data showing that venlafaxine, a serotonin and norepinephrine reuptake inhibitor, but not

placebo, induced an increase in LDL-C in social phobic patients,[26] suggest a possible role for the inhibition of serotonin reuptake in the increase of LDL-C.

Limitations of the present study include the administration of paroxetine at only the minimal therapeutic dose of 20 mg/day, the short duration of paroxetine administration justified by the fact that it was administered to healthy volunteers, and the exclusion of females.

It remains to be determined whether the paroxetine-induced increase in LDL-C is persistent or temporary. In fact, the results of our less strictly controlled pilot study in panic disorder patients favor a persistent and perhaps greater effect over time since the average duration of administration of SSRIs varied from 4.5 to 13.5 months in that study.[14] The persistence of the paroxetine-induced increase in LDL-C would be particularly worrisome since, after the occurrence of 2 or more relapses of major depressive episodes, lifetime pharmacologic treatment with antidepressants is recommended in MDD patients.[10]

Although expected, it will be essential to investigate whether paroxetine-induced increases in LDL-C also take place in cardiac patients with MDD or anxiety disorders, a population in which a moderate increase would be of greater concern and might justify therapeutic intervention with a lipid-lowering therapy. The recent evaluation of the safety and efficacy of sertraline in the treatment of MDD in patients with acute myocardial infarction or unstable angina reported no clear impact on cardiovascular outcomes.[27] This difficulty in showing a positive effect of sertraline on cardiovascular outcomes might have been related to potential deleterious cardiovascular effects of sertraline such as increases in LDL-C levels. The lack of a clear beneficial impact of SSRIs on cardiovascular outcomes could result from the antagonism between their beneficial and unknown deleterious effects such as an induced increase in cholesterol.

Although the impact of antidepressant treatment on cardiovascular outcomes in patients with MDD remains to be determined, administration of cholesterol-lowering agents rather than discontinuation of the antidepressant paroxetine to manage paroxetine-induced elevated cholesterol levels would not be unreasonable (when required by NCEP guidelines) since MDD itself is associated with an increased risk for CHD and cardiovascular events. There are no pharmacokinetic studies in the literature on the combination of paroxetine and statins, the most frequently prescribed cholesterol-lowering agents. However, from what is known about their respective drug metabolism, statins and paroxetine are unlikely to interact with each other. Indeed, paroxetine inhibits cytochrome P450 2D6, whereas metabolism of statins is inhibited by drugs that inhibit cytochrome P450 3A enzymes.

In summary, we have shown that 8 weeks of paroxetine administration, at minimal therapeutic doses, induces a moderate increase in LDL-C levels in male healthy controls without associated CHD risk factors. The magnitude of the paroxetine-induced increase in LDL-C, although most likely associated with a minimal CHD risk in a minority of subjects, would not warrant therapeutic intervention in most patients without CHD. On the contrary, the same increase in LDL-C levels would lead to therapeutic intervention aimed at lowering LDL-C in patients with established CHD and MDD. Our findings need to be confirmed in a larger sample as well as in a population of patients suffering from CHD and MDD or anxiety disorders.

Drug names: paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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