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ORIGINAL ARTICLE

Orlistat Abolishes Postprandial Lipid Peaking

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Postprandial hyperlipemia is associated with the development of cardiovascular disease. Orlistat is a pancreatic lipase inhibitor that reduces fat absorption from the diet by inhibition of hydrolysis of triglycerides. Since the effect of orlistat on postprandial lipemia has not been fully elucidated, we studied the effect of orlistat on postprandial lipemia after a 50% oral fat challenge test (OFCT). Materials and Methods: Twenty-seven healthy volunteers, aged 18-45 years old, with normal body mass index (BMI) and normal fasting lipid levels, were studied. The control group (n=15) was given the 50% OFCT while the study/orlistat group (n=12), was given 120 mg orlistat followed by intake of the 50% OFCT. Total cholesterol (TC), triglycerides (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) were determined at baseline and serially over a 6-hour period. Results: In the control group, TC, TG and HDL peaked in the 4th hour. This lipid peaking was not observed in the orlistat group. Percentage change between baseline to the 4th hour values in the control vs. the study group were, respectively, as follows: TC = 65.80% vs. -1.60%; TG = 262.64% vs. 24.74%; and HDL = 205.26% vs. -1.43%. The mean postprandial levels for TC, TG and LDL were well within the normal fasting cut-offs of <6.20 mmol/L, <2.26 mmol/L, and < 4.14 mmol/L respectively throughout the entire 6-hour study period. Conclusion: Orlistat abolished the peaking of TC, TG, and HDL after a 50% OFCT. Nonetheless, lipid values were maintained within normal fasting levels in the orlistat group.

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Introduction

Postprandial lipemia has been offered as an explanation for the presence of cardiovascular disease among patients with normal fasting lipids. Recent reviews cite several clinical trials which have shown that the magnitude and duration of postprandial lipemia is positively related to the pathogenesis and progression of coronary heart disease.[1-2] An elevated postprandial lipemic response causes endothelial dysfunction, production of atherogenicsmall,denselow-density lipoprotein (LDL) particles and modification of hemostatic variables promoting thrombosis.[3-6]

In 2003, So et al studied the lipid profile of healthy Filipinos after an oral fat challenge test (OFCT) using mixed fatty meals with 40%, 45% and 50% fat.[7] Results show that there was a doubling from fasting levels for total cholesterol (TC), triglycerides (TG) and high-density lipoprotein (HDL), in the 4th to 5th hour, with a descent commencing in the 6th hour; however for LDL, it nadirs in the 2nd hour for the 50% OFCT and in 5th hour for both the 40% and 45% OFCT.

Orlistat is a pancreatic lipase inhibitor that specifically reduces fat absorption from the diet due to inhibition of hydrolysis of trigly-

cerides. As a consequence, about 30% of dietary triglycerides remain undigested and are not absorbed.[8] Improvement in the lipid profile has been shown using this agent. [8-10] However, majority of the studies utilized fasting lipid levels.

The objective of this study is to determine the effect of orlistat on postprandial lipemia after a 50% oral fat challenge test among healthy, normolipidemic individuals.

Materials and methods

Study subjects: Two groups of subjects were studied; the first, consisting of 15 adult volunteers, was studied a few years earlier than the second group, consisting of 12 volunteers. For both groups, the inclusion criteria were male or female, 18-45 years old, with normal BMI[11] of 18.5-22.9 kg/m^2 and normal fasting lipid levels.[12-13] Excluded were those with any clinical evidence of coronary artery disease, peripheral artery disease, diabetes mellitus, hepatic or renal disease, dyslipidemia, acute or chronic medical conditions; those on any maintenance medications, pregnant individuals, those who had donated blood in the past three months or those with menstruation at the time of the study. Subjects were evaluated for complete blood count, fasting plasma glucose (FPG), creatinine, total protein, albumin, globulin, ALT, TC, TG, LDL and HDL. Written informed consent was obtained from all participants. The study was conducted in a tertiary hospital in accordance with the ethical principles set forth in the Declaration of Helsinki.

Preparation of the oral fat challenge test: A mixed meal type of oral fat challenge test (OFCT) consisting of 3 slices of bread and butter was prepared by a single dietician according to the subject's daily caloric requirement. The subject's desired body weight (DBW) was computed from the subject's height according to the Tannhausser's (Broca) Method[14].

DBW (kg) = [Height (cm) – 100] – 10% for Filipino stature.

The total daily caloric requirement (TCR) was then computed by multiplying the subject's DBW with his caloric requirement (cal/kg DBW/day) according to his activity level.[14] The TCR was then subdivided into 50% fat, 45% carbohydrate and 5% protein. One-third of this, representing one of the three main meals in a day, constituted the OFCT that was given to the subjects. For every 5 grams of fat load requirement, 1 teaspoon of melted butter was given to the subject. This was spread over 2-3 slices of bread.

OFCT and orlistat administration: The subjects were asked to report at a designated place at 7 am after a 12-hour fasting period. Heplock was inserted to facilitate the serial blood extractions. After the first/baseline blood extraction, the participants of the orlistat arm (n=12) were asked to take 1 capsule of orlistat (Xenical) 120 mg per orem followed by the 50% OFCT. The control group (n=15) took the OFCT only. Plasma lipid profile was determined serially at baseline (point 0) and following the 1st, 2nd, 3rd, 4th, 5th and 6th hour. All subjects were instructed to observe for oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation and fecal incontinence for the next 2 days.

Laboratory methods: Blood samples were collected in tubes containing EDTA. Samples were centrifuged and the plasma was stored by refrigeration and was analysed within 24 hours. Levels of total cholesterol, triglycerides and HDL were measured enzymatically on a Hitachi 902 autoanalyzer (Roche Diagnostics). The Friedewald equation [(total cholesterol – HDL cholesterol) – (triacylglycerol/2.2)] was used to calculate LDL cholesterol. The coefficients of variation for lipid values across the 6-hour study period are as follows: TC: 3.8-15.5%, TG: 6.4-55.4%, HDL: 11.5-46.5%, LDL: 8.0-65.8%.

Statistical analysis: All tests of significance were performed using the Statistical

Package for the Social Sciences (SPSS Version 14, Chicago Ill). Descriptive statistics include mean and their standard deviation. Testing sample homogeneity at baseline was done using Mann Whitney U test for the skewed distribution of lipid values and the inherent small sample size requirement. Within groups comparison for repeated measurements was performed using Wilcoxon Signed Ranks test. All tests of significance were pegged at 0.05 level of significance.

Results

A total of 27 healthy Filipino volunteers met the inclusion criteria and were included in the final analysis. No dropouts were noted. Table 1 summarizes the baseline characteristics of the 2 groups. The age, BMI, FPG, creatinine and ALT of the 2 groups were similar. A statistically higher mean baseline TC level was observed in the control group compared to orlistat group (mean = 5.0 versus 4.37 mmol/L, $p < 0.001$). Likewise, baseline mean LDL was noted to be statistically higher in the control group (mean = 3.12 versus 2.52 mmol/L, $p < 0.001$). On the other hand, a statistically higher baseline mean HDL was noted in the orlistat group (mean=1.41 versus 0.95 mmol/L, $p < 0.001$). Baseline mean TG levels were similar between the 2 groups (0.91 versus 0.97 mmol/L, $p = 0.63$).

Table 1. Baseline characteristics of the control and orlistat groups[a]

Characteristics	No orlistat (n= 15)	With orlistat (n=12)
Age (yrs)	28.4±3.9	26.8±4.7
BMI (kg/m^2)	20.6±1.5	21.2±1.2
FBS (mmol/L)	5.3±0.3	5.2±0.5
Creatinine (µmol/L)	74.2±3.1	73.6±4.0
ALT (u/L)	29.8±15.6	27.0±7.2
Total Cholesterol (mmol/L)	5.0±0.2	4.3±0.6*
Triglycerides (mmol/L)	0.91±0.13	0.97±0.44
High density lipoprotein (mmol/L)	0.95±0.12	1.41±0.27*
Low density lipoprotein (mmol/L)	3.1±0.2	2.52±0.48*

A: Data are mean ± SD; *: P<0.001, BMI: body mass index, FBS: fasting blood sugar, ALT: alanine transferase.

Total Cholesterol: Table 2 shows a summary of the change in mean TC at different time points in the control and the orlistat groups. In the control group, statistically significant hourly elevations of TC were noted at all time points beginning at baseline up to the 4th hour (all p=0.001). TC remained elevated at the 5th hour with a value not statistically different from that of the 4th hour. The highest peak was noted during the 4th and 5th hours postprandial (mean=8.29±0.74 and 8.32±0.51 mmol/L, respectively). Mean TC level was noted to decline in the 6th hour with a value significantly lower than that of the 5th hour (p=0.001). In contrast, no statistically significant elevation of TC was noted at any point in the orlistat group. In this group, a significant drop in mean TC level was noted between baseline and first hour ($p = 0.001$) values, with no significant change in mean TC levels thereafter.

Table 2. Comparison of mean total cholesterol, triglycerides, HDL and LDL levels across time within group and between groups

LIPID	GROUP	Baseline	1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	p-value[b]
TC	Control	5.00±0.19	5.66±0.39**	6.68±0.63**	7.67±0.80**	8.29±0.74**	8.32±0.51	7.55±0.98**	0.001
	Orlistat	4.37 ± 0.61	4.13 ± 0.61**	4.24 ± 0.66	4.22 ± 0.58	4.30 ± 0.60	4.40 ± 0.65	4.34 ± 0.62	0.001
	Difference[c]	0.63	1.53	2.44	3.45	3.99	3.92	3.21	--
	P value[a]	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
TG	Control	0.91±0.12	1.77±0.27**	2.67±0.17**	3.00 ± 0.23**	3.30±0.31**	3.13±0.42**	2.81±0.56**	<0.001
	Orlistat	0.97 ± 0.44	0.95 ± 0.44	1.10 ± 0.61**	1.20 ± 0.60	1.21 ± 0.59	1.11±0.44**	0.94±0.36**	<0.001
	Difference[c]	-0.06	0.82	1.57	1.80	2.09	2.02	1.87	--
	P value[a]	0.63	<0.001	0.045	<0.001	<0.001	<0.001	<0.001	
HDL	Control	0.95±0.11	1.61±0.31**	2.29±0.34**	2.60±0.41**	2.90±0.48**	2.84 ± 0.48	2.49±0.48**	<0.001
	Orlistat	1.40 ± 0.27	1.33 ± 0.30**	1.35 ± 0.29	1.36 ± 0.30	1.38 ± 0.31	1.39 ± 0.31	1.45±0.27**	<0.001
	Difference[c]	-0.45	0.28	0.94	1.24	1.52	1.45	1.04	--
	P value[a]	<0.001	0.004	<0.001	<0.001	<0.001	<0.001	<0.001	
LDL	Control	3.12 ± 0.25	2.30 ± 0.38**	1.68 ± 0.87	2.10 ± 1.10	2.20 ± 1.04	2.53 ± 1.30	2.43 ± 1.60	<0.001
	Orlistat	2.52 ± 0.48	2.37 ± 0.41**	2.40 ± 0.48	2.33 ± 0.45	2.40± 0.47**	2.42±0.48	2.50±0.45**	<0.001
	Difference[c]	0.60	-0.07	-0.72	-0.23	-0.20	0.11	-0.07	
	P value[a]	0.001	0.98	0.004	0.46	0.27	0.94	0.78	

Significant difference: p value <0.05, [a]between groups comparison by Mann Whitney U test, [b]within group comparison by Wilcoxon Signed Ranks test, [c]difference between groups, ** significant change from previous hour within group. TC: total cholesterol, TG: triglycerides.

Comparing the two groups, the mean TC levels were significantly higher in the control group at all time points (all $p < 0.001$). The greatest mean difference was noted during the 4th hour postprandial. (Table 2)

Serum triglycerides: Shown in Table 2 is a summary of the change in mean TG levels at different time points in the control and the orlistat groups. In the control group, statistically significant hourly elevations of TG were noted at all time points beginning at baseline up to the 4th hour (all $p < 0.001$). The highest peak was noted during the 4th hour postprandial (mean = 3.3 ± 0.31 mmol/L). A significant decline in TG level was noted in the 5th hour with a further drop noted in the 6th hour ($p < 0.001$). For the orlistat group, a significant rise in TG level was noted only at one point – between the 1st and the 2nd hour ($p < 0.001$) and a significant drop was noted beginning in the 5th hour with a further drop observed in the 6th hour ($p < 0.001$).

Comparing the two groups, TG levels were similar at baseline ($p = 0.63$). Thereafter, TG levels were significantly lower in the orlistat group at all time points ($p = 0.045$ in the 2nd hr, $p < 0.001$ at all other time points). The greatest mean difference was noted during the 4th hour postprandial. (Table 2)

Serum high density lipoprotein: Table 2 shows a summary of the change in mean HDL at different time points in the control and the orlistat groups. In the control group, statistically significant hourly elevations of HDL were noted at all time points beginning at baseline right up to the 4th hour (all $p < 0.001$). HDL remained elevated in the 5th hour with a value not statistically different from that of the 4th hour. The highest peak was noted during the 4th and 5th hours postprandial (mean = 2.9 ± 0.48 and 2.84 ± 0.48 mmol/L). Mean HDL was seen to decline in the 6th hour with a value significantly lower than that of the 5th hour ($p<0.001$). However, in the orlistat group, a significant drop was noted the first hour ($p < 0.001$) and a significant rise was seen during the 6th hour relative to the 5th hour value ($p < 0.001$).

Comparing the two groups, values for the orlistat group were statistically lower ($p = 0.004$ on the 1st hr, $p < 0.001$ at all the other time points). The greatest mean difference between the control and orlistat groups occurred during the 4th hour postprandial. (Table 2)

Serum low density lipoprotein: Table 2 shows a summary of the change in mean LDL levels at different time points in the control and the orlistat groups; for the control group, postprandial values were noted to be lower than the baseline value, with the lowest value noted in the 2nd hour. For the orlistat group, LDL levels were noted to be either lower or equal to the baseline level. (Table 2)

Table 3 summarizes the characteristics of postprandial lipemia with and without orlistat; without orlistat, TC, TG and HDL were noted to peak in the 4th to 5th hour with 66.4, 262 and 205% increase in baseline values, respectively. TC and HDL started to decline in the 6th hour, whereas TG started to decline in the 5th hour. Following use of orlistat, no peaking of TC, TG and HDL was noted and the percentage change from baseline to the 4th hour was -1.60%, 24.74% and -1.43% respectively. Furthermore, the 4th hour mean TC, TG and HDL levels of the control group were twice that of the orlistat group with values for the control vs. the orlistat group being as follows: TC = 8.29±0.74 vs. 4.30±0.60; TG=3.30±0.31 vs. 1.21±0.59; HDL=2.90± 0.48 vs. 1.38±0.31. (Table 3)

Although postprandial lipid peaking was not noted in the orlistat group, the mean postprandial levels for TC, TG and LDL were well within the normal fasting cut-offs of <6.20 mmol/L, <2.26 mmol/L, and < 4.14 mmol/L12,13 respectively throughout the entire 6-hour study period.

Table 3. Characteristics of postprandial lipids in the control and orlistat groups

Lipid	Baseline (mmol/L)		Time of peak (hour)		Mean level on the 4th hour (mmol/L)		% change from baseline to peak		Onset of decline (hour)	
	Control	Orlistat	Control	Orlistat	Control	Orlistat	Control	Orlistat	Control	Orlistat
Total Cholesterol	5.0±0.2	4.4±0.6	4th to 5th	None	8.3±0.7	4.3±0.6	66.4	-1.6%	6th	NA
Triglycerides	0.9±0.1	0.9±0.4	4th	None	3.3±0.3	1.2±0.6	263	24.7%	5th	NA
HDL	0.9±0.1	1.4±0.3	4th to 5th	None	2.9±0.5	1.4±0.3	205	-1.4%	6th	NA

Side effects of orlistat: Five of the twelve (41.67%) subjects reported a maximum of 2 adverse events, described as mild and tolerable. The reported adverse events were confined to the gastrointestinal tract, all occurring within 30 hours from intake of orlistat. Four had oily stools, 2 had oily spotting, and 1 had flatus with discharge. All symptoms were self-limited, occurring only once.

Discussion

Since studies linking elevated lipid levels to cardiovascular disease have traditionally used fasting lipid values, in clinical practice, cholesterol, triglycerides, HDL and LDL are usually determined after a 10 to 12-hour fast.[12-13] In reality, however, most people are in their postprandial state for much of the day and a significant part of the night. As shown in this study, both total cholesterol and triglycerides gradually increase postprandially, reaching peak levels in the 4th to 5th hour and then begin to decline in the 5th or 6th hour when we usually start to have our next meal. This means that high levels of cholesterol and triglyceride are sustained during the waking hours with the next meal being introduced even before lipid levels could go down to baseline levels from the previous meal. The impact and influence of postprandial hyperlipemia in the development of cardiovascular disease has been underestimated.

Indeed, postprandial lipemia is an emerging risk factor for cardiovascular disease. Two recent studies have shown that nonfasting triglyceride levels are associated with increased risk of cardiovascular events and death.[15-16] The first is a prospective study, conducted in Denmark, involving 7,587 women and 6,394 men with a 26 year follow-up.[15] Like our study, triglyceride levels were noted to peak 4 hours after the last meal and they concluded that elevated nonfasting triglyceride levels were associated with increased risk of myocardial infarction, ischemic heart disease and total mortality in both men and women. The second study involved 26,509 initially healthy American women participating in the Women's Health Study with median follow-up of 11 years.[18] They reported that nonfasting triglyceride levels were associated with cardiovascular events, independent of traditional cardiac risk factors, levels of other lipids, or markers of insulin resistance; in contrast, fasting triglyceride levels showed little independent relationship. Moreover, triglyceride levels measured 4 hours postprandially had the strongest association with cardiovascular events. This coincides with the time of triglyceride peaking noted in our study.

Interest on the role of postprandial hyperlipemia in the development of cardiovascular disease has already led to several investigations on the effect of lipid-lowering agents on postprandial lipid concentrations.[17-28] Most of these studies have been performed with either fibrates or statins. Fibrates are thought to increase the rate of removal of postprandial triglycerides by the peroxisomal proliferators activated receptor (PPAR) alpha-stimulated increase of lipoprotein lipase activity,[29] whereas, statins are thought to increase the num-

ber of LDL receptors which may improve the clearance of triglyceride-rich lipoprotein and chylomicron remnants in the postprandial state.[28-29]

Our study was done to determine the effect of the pancreatic lipase inhibitor, orlistat on postprandial lipemia, and to evaluate the clinical utility of orlistat as an anti-lipid drug that could lower the postprandial lipemic response to a fatty meal.

This study has shown that without orlistat, postprandial lipid peaking occurs. However, ingestion of orlistat with a meal led not only to a lower postprandial lipemic response but to total abolition of postprandial lipid peaking.

Orlistat abolished the peaking of TC, TG, and HDL after a 50% OFCT. Nonetheless, lipid values were maintained within normal fasting levels in the orlistat group.

The postprandial lipid-lowering effect of orlistat may be explained by its ability to inhibit the hydrolysis of dietary triglycerides into the more absorbable free fatty acids (FFAs) and monoglycerides, leading to a decrease in the absorption of triglycerides at the level of the small intestine.[8] Furthermore, the solubility of cholesterol also decreases in direct proportion to decreasing amounts of FFAs and monoglycerides in the intestine, so that orlistat also indirectly decreases the absorption of cholesterol.[8]

To conclude, clinically, the results of this study imply that orlistat may be used not only for reduction of weight but also for control of postparandial lipid elevations. Thus, it may serve as a drug for primary prevention of cardiovascular disease.

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