THE EFFECTS OF CLARITROMYCIN ADDED TO ATORVASTATIN TREATMENT ON SERUM LIPID PROFILES: A randomised clinical trial

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ABSTRACT

Purpose: The effect of claritromycin added to atorvastatin in treatment of dislipidemia have been investigated and compared to the effects of atorvastatin monotherapy.

Methods: 120 hyperlipidemic patients who met inclusion criteria were sampled from Internal Medicine Outpatient Clinic of the Medical School Hospital in Sivas, Turkey and were randomized into two treatment protocols. Atorvastatin (40mg/day for 6 weeks) + Claritromycin (500mg/day for 2 weeks) treatment was given to patients in the first group. Atorvastatin (40mg/day) treatment was given to patients in the second group for 6 weeks. Lipid profiles, fibrinogen, C-reactive protein (CRP) were studied before starting treatment and repeated at the end of 6 weeks treatment period. The data analysis was performed by using descriptive statistics, Independent-Samples 't' test and Paired-Samples 't' test.

Results: The mean age of 60 cases in the first group was 53.40±2.25 years and it was 55.15± 8.4 years in the second group. Demographics of gender, the mean ages and pretreatment values of triglyceride, total cholesterol, HDL- cholesterol, LDL- cholesterol, CRP and fibrinogen; the differences between two groups were not statistically significant ($p>0.05$). When the parameters were compared between two groups for the post treatment values, the differences were statistically significant ($p<0.05$), except of triglyceride ($p>0.05$). The decrease in CRP and fibrinogen and increasing in HDL- cholesterol were higher in the first group compared to those in the second group. The decreasing in total and LDL-cholesterol were higher in the second group compared to those in the first group.

Conclusion: Adding claritromycin to the statin treatment in dislipidemic patients has no favorable effect on total and LDL- cholesterol levels. However, it has a favorable effect on HDL-cholesterol levels CRP and fibrinogen. However, routine addition of antibiotics to statin therapy cannot be recommended at present.

KEYWORDS: Claritromycin, HDL- cholesterol, LDL- cholesterol.

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INTRODUCTION

Chlamydia pneumoniae (CP) is an intracellular Gram-negative bacterium that commonly causes respiratory infections. CP infection has been associated with atherosclerosis in seroepidemiological studies, and the organism was found within atherosclerotic lesions.[1,2] These observational evidences of the association are further supported by pilot intervention studies which indicate substantial reductions in secondary ischaemic events in survivors of myocardial infarction treated with antibiotics effective against CP.[3] The underlying processes

of the association between infectious agents and atherosclerotic disease remain unclear. Various potential pathomechanisms have been postulated; increased production of cytokines and acute-phase reactants, local or systemic disturbance of fibrinolysis and blood coagulation, direct infection of the arterial wall via macrophages and alteration of vascular cell function, and an immunological response (cross-reaction) due to bacterial heat shock protein.[4-6] Because it is well known that acute infections are able to modify serum lipids, some authors have also suggested that alterations of the lipid metabolism due to chronic infections could represent an atherogenic link.[7-12] Elevated levels of total cholesterol and triglycerides and decreased HDL cholesterol concentration were reported for subjects with seropositivity to CP[7-9] or *Helicobacter Pylori* (HP)[10,11]. However, none of the studies evaluating the role of antibiotic therapy in arteriosclerosis have examined the effects of antibiotic therapy on serum lipid profiles.[13] In this study, the effect of claritromycin added to atorvastatin in treatment of dislipidemia have been investigated and compared to the effects of atorvastatin monotherapy.

METHODS

Between September 2001 and December 2002, 120 patients who met following inclusion criteria were sampled from Internal Medicine Outpatient Clinic of the Medical School Hospital in Sivas, Turkey.

Inclusion Criteria:

1. Patients requiring antihyperlipdemic drug treatment according to NCEP guidelines (total cholesterol >220 mg/dl and LDL > 130 mg/dl in their venous blood after a 12 hours fasting period) who had positivity for *Chlamydia pneumoniae* IgG.
2. They should not have lipid lowering treatment in the previous three months before the initiation of study.
3. Patients have no allergy history against statins and macrolides.
4. Patients without a malignancy or serious disease or surgical intervention within the last three months and have not any acute infection.
5. They have no liver disease (normal transaminase levels), muscle or endocrine disease (hyperthyrodism, Cushing's syndrome, and acromegaly) renal failure, proteinuria (over 1 g/day). No one had alcohol and tobacco usage history.
6. The patients have no uncontrolled arterial hypertension (systolic blood pressure >180 mmHg or diastolic blood pressure >100 mmHg).
7. Patients taking corticosteroids ,administering antiacids within three hours after statin intake, patients recieving aspirin or coumadin type anticoagulants, immunosuppresive drugs, other lipid lowering drugs, other antibiotics, digitalis and nonsteroid anti-inflammatory drugs were excluded from the study.

The patients were randomized into two treatment groups. Atorvastatin (40mg/day for 6 weeks) + Claritromycin (500mg/day for 2 weeks) treatment was given to patients in the first group. Atorvastatin (40mg/day) treatment was given to patients in the second group for 6 weeks. Blood samples was obtained from forearm weins after 12 hours fasting period. Lipid profiles, fibrinogen, C-reactive protein (CRP), were studied before starting treatment and repeated at the end of 6 weeks treatment period. By using standart laboratory methods and commerical kits; thyroidal function test, liver and renal function tests, muscle enzymes and Complete Blood Count (CBC) tests were performed to exclude secondary hyperlipidemia. Lipid profiles were studied by using IL ab 900/1800 device and IL Cholesterol and Triglyceride kits. Fibrinogen was studied by clotting method on STA Compact (Franvel) device using STA Fibrinogen - (Diagnostica Stage, France) kit. CRP was studied by turbidimetric measurement method on Space (Italy) device using ACE TM reagent for CRP (Schiapprelli. Biosystems, BV. The Netherlands) kit. *Chlamydia pneumoniae* IgG serology

was studied by ELISA method on TRITURUS named automatic device using Vircell (Spain) kit.

The Ethical Committee of Cumhuriyet University approved the study procedure. Written consent was obtained from all of the patients included in the study. The data analysis was performed on SPSS (ver 9.05) by using descrip tive statistics, Independent-Samples 't' test and Paired-Samples 't' test. The results were given as mean ± standard deviation (X±SEM). Statistical significance was accepted as "p<0.05".

RESULTS

The mean age of 60 cases in the first group was 53.40± 2.25 years (33 males, 27 females) and it was 55.15± 8.4 years (29 males, 31 females) in the second group. Upon on gender and the mean ages; the differences between two groups was not statistically significant (p>0.05). The differences between two groups was also not statistically significant upon on pretreatment values of triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, CRP and fibrinogen (Table-I) (p>0.05). When the parameters were compared between two groups by the post-treatment values, the differences were statistically significant (p<0.05), except of triglyceride (p>0.05). The decrease in CRP and fibrinogen and increase in HDL-cholesterol were higher in the first group (atorvastatin+claritromycin combination therapy) compared to those in the second group (atorvastatin monotherapy). However, the decrease in total cholesterol and LDL- cholesterol were higher in the second group compared to those in the first group (Table-I). When the pre- and post-treatment values were compared within the groups, the differences of all parameters were statatisticlly significant in both groups (p<0.05) (Tables II and III).

DISCUSSION

Elevated levels of total cholesterol and triglycerides and decreased HDL cholesterol

Table-I: Parameters of the groups compared by pre - and post treatment values (Between groups comparison)

Parameters	*Group 1*	*Group 2*	*p Value*
Cholesterol*	270.50±44.54	260.43±33.97	0.167
Cholesterol**	200.13±44.92	174.50±39.49	0.001
Triglycerides*	231.45±64.87	227.55±63.35	0.740
Triglycerides**	170.63±54.53	166.58±49.12	0.670
HDLChol*	42.95±8.62	40.77±6.30	0.116
HDLChol**	45.23±7.47	41.60±7.77	0.010
LDLChol*	168.18±20.75	163.65±21.01	0.237
LDLChol**	124.40±27.97	112.92±28.0	0.026
CRP*	12.65±11.73	10.58±5.50	0.219
CRP**	8.42±5.09	6.25±4.18	0.012
Fibrinogen*	353.15±87.13	351.93±97.78	0.943
Fibrinogen**	300.05±69.26	329.07±85.77	0.044

* pre-treatment values
** post-treatment values

Table-II: Parameters of the first group (atorvastatin+claritromycin) compared by the pre and post treatment values (Within group comparison)

Parameters	*Pre-treatment values*	*Post-treatment values*	*p Value*
Cholesterol	270.50±44.54	200.13±44.92	0.005
Triglycerides	231.45±64.87	170.63±54.53	0.005
HDL-Chol	42.95±8.62	45.23±7.47	0.005
LDL-Chol	168.18±20.75	124.40±27.97	0.004
CRP-Chol	12.65±11.73	8.42±5.09	0.005
Fibrinogen	353.15±87.13	300.05±69.26	0.005

Table-III: Parameters of the second group (atorvastatin mono-therapy compared by pre and post treatment values (within group comparison)

Parameters	*Pre- treatment values*	*Post-treatment values*	*p Value*
Cholesterol	260.43±33.97	174.50±39.49	0.054
Triglycerides	227.55±63.35	166.58±49.12	0.005
HDL-Chol	40.77±6.30	41.60±7.77	0.005
LDL-Chol	163.65±21.01	112.92±28.00	0.005
CRP	10.58±5.50	6.25±4.18	0.005
Fibrinojen	351.93±97.78	329.07±85.77	0.005

concentration were reported for subjects with seropositivity to CP.[7-9] The CP IgG antibody positivity in a subject suggests that CP has infected before him/her or had a persistent infection.[14] If these infections contribute even partly to the altered serum lipid profile, eradication of the infection by antibiotic treatment would add benefits to the standard statin treatment in dislipidemic patients with positivity of CP specific IgG antibodies. In a simple pragmatic design, present study tested this hypothesis and it is the first reported study examining the value of antibiotherapy in dislipidemic patients. In this study, we found a significant additional benefits of antibiotherapy in increasing of HDL-cholesterol and in decreasing of CRP and fibrinogen compared to the statin monotherapy. Fibrinogen and CRP were used as intermediate markers in the present study, as they have emerged as the most effective markers of antibiotic treatment in earlier studies.[15] However, the decrease in total cholesterol and LDL-cholesterol levels were higher in the statin monotherapy group compared to those in the combination therapy group. Since the major component of dislipidemia is represented by total cholesterol and LDL-cholesterol, we concluded that additional benefits of antibiotherapy in dislipidemia is limited.

CONCLUSION

Our results indicate that adding claritromycin to the statin treatment in dislipidemic patients has no favorable effect on total cholesterol and LDL-cholesterol levels. However, it has a favorable effect on HDL-cholesterol levels and on predictors of inflamation such as CRP and fibrinogen. Further studies are, therefore, needed to clarify whether antibiotic therapy has any beneficial effects in treatment of dislipidemic patients. At this stage, the addition of antibiotics routinely to lipid-lowering therapy cannot be recommended.

REFERENCES

1. Grayston JT, Kuo CC, Wang SP, et al. A new Chlamydia psittaci strain, TWAR, isolated in acute respiratory tract infections. N Engl J Med 1986; 315:161-8.
2. Ward ME. The immunobiology and immunopathology of chlamydial infections. APMIS 1995; 103:769-96.
3. Murray LJ, O'Reilly DPJ, Ong GML, Evans AE, Bamford KB. *Chlamydia pneumoniae* antibodies are associated with an atherogenic lipid profile. Heart 1999;81:239–44.
4. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet. 1997;350:430–6.
5. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. Circulation 1997; 96:4095–103.
6. Mehta JL, Saldeen TGP, Rand K. Interactive role of infection, inflammation and traditional risk factors in atherosclerosis and coronary artery disease. J Am Coll Cardiol 1998; 31:1217–25.
7. Laurila A, Bloigu A, Näyhä S, Hassi J, Leinonen M, Saikku P. Chronic *Chlamydia pneumoniae* infection is associated with a serum lipid profile known to be a risk factor for atherosclerosis. Arterioscler Thromb Vasc Biol 1997; 17:2910–13.
8. Laurila A, Bloigu A, Näyhä S, Hassi J, Leinonen M, Saikku P. *Chlamydia pneumoniae* antibodies and serum lipids in Finnish men: cross sectional study. BMJ 1997; 314:1456–7.
9. Murray LJ, O'Reilly DPJ, Ong GML, Evans AE, Bamford KB. *Chlamydia pneumoniae* antibodies are associated with an atherogenic lipid profile. Heart 1999;81:239-44.
10. Niemelä S, Karttunen T, Korhonen T, Läärä E, Karttunen R, Ikäheimo M, et al. Could *Helicobacter pylori* infection increase the risk of coronary heart disease by modifying serum lipid concentrations? Heart 1996; 75:573–5.
11. Laurila A, Bloigu A, Näyhä S, Hassi J, Leinonen M, Saikku P. Association of *Helicobacter pylori* infection with elevated serum lipids. Atherosclerosis 1999; 142:207–10.
12. Nieto FJ, Sorlie P, Comstock GW, Wu K, Adam E, Melnick JL, Szklo M. Cytomegalovirus infection, lipoprotein (a), and hypercoagulability: an atherogenic link? Arterioscler Thromb Vasc Biol 1997;17:1780–5.
13. Boman J, Hammerschlag MR. Chlamydia pneumoniae and atherosclerosis: critical assessment of diagnostic methods and relevance to treatment studies**.** Clin Microbiol Rev 2002; 15(1):1-20.
14. Saikku P, Leinonen M, Mattila K, Ekman MR, Nieminen MS, Mäkelä PH, Huttunen J, Valtonen V. Serologic evidence of an association of a novel *Chlamydia*, TWAR, with chronic coronary heart disease and acute myocardial infarction. Lancet 1988; 2:983-5.
15. Higgins PJ. Chlamydia pneumoniae and coronary artery disease: The Antibiotic Trials. Mayo Clin Proc 2003; 78:321-32.