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ORIGINAL ARTICLE

Action of statins upon thrombogenesis, fibrinolysis and inflammation in coronary patients

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It has been established that the use of statins and application of a healthy modified diet and way of life have a favorable influence upon lipids, fibrinogen, PAI-1, t-PA, and C-reacting protein (CRP) in hyperlipidaemic patients with angina manifestations.

We studied 206 hyperlipidaemic patients (phenotypes IIa and IIb, according to Fredricson) of both sexes (M=116, F=90, mean age 51.7+ 6.8 years) hospitalized in our department with angina manifestations. Group A consisted of 65 patients, 44 with stable angina (M=31, F=13) and 21 with unstable angina (M=12, F=9), treated with pravastatin 20 mg daily while Group B consisted of 141 patients, 112 with stable angina patients (M=62, F=60) and 29 with unstable angina (M=13, F=16), treated with fluvastatin 40 mg daily. Patients with conditions affecting the acute inflammatory proteins were excluded from the study. All patients followed a specific diet for three months at the same time as antilipidaemic treatment was administered. At the end of the three months period, all patients underwent the same clinical, biochemical and electrocardiographic estimation as at baseline.

The concurrent application of our healthy modified model of diet and living and antilipidaemic drug treatment for three months resulted to: 1) A statistically significant reduction of total-ch, triglycerides, LDL-ch levels and significant elevation of LDL-ch compared to those at baseline. 2) A reduction of fibrinogen levels: 7.9% in the fluvastatin group ($p<0.05$) and 4.8% in pravastatin group. 3) A statistically significant reduction of PAI-1 levels and a statistically significant elevation of t-PA levels compared to those at baseline. 4) A statistically significant elevation ($p<0.001$) of CRP levels at baseline in patients with unstable angina compared to those with stable angina and with normal values. 5) A greater reduction ($p<0.05$) of CRP levels after three months' treatment with pravastatin compared to those with fluvastatin. 6) A good long-term outcome for all patients. Thirty-two patients from the group with unstable angina had a positive for CAD exercise test (Ex) performed one month after discharge whilst the remaining 8 had an uncertain or negative Ex. 24 of them underwent coronary angiography with stenotic lesions < 50% in one or two arteries. Drug treatment was continued and an appointment after six months was recommended. 7) A non-statistically significant elevation within normal levels of SGPT, SGOT, CpK-MB. The levels of serum glucose and the other biochemical parameters were not influenced. 8) Gastroenteritis in six patients which was managed without interruption in the administration of the antilipidaemic drug.

The combination of a hypolipidaemic diet, regular exercise, cessation of smoking, loss of body weight and hydrophilic statins seems to act favorably on hyperlipidaemic coronary patients improving clinical status and anatomic lesions. This action is achieved by functionally improving the endothelium, suppressing the inflammation, reducing the thrombogenesis, supporting the fibrinolysis and decreasing the lipid levels.
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It is a well-established fact that hyperlipidaemia is a major risk factor for coronary arterial disease (CAD) development. The reduction of blood lipid levels by antilipidaemic drugs, modification of diet, and application of a healthier way of life is associated with retardation in process of CAD and improvement of its clinical manifestations[1-3].

Relatively new independent CAD risk factors

with prognostic significance such as cells (macrophages, platelets, T-lemphocytes, smooth muscle cells), coagulation-fibrinolysis factors (tissue plasminogen activator, plasminogen activator inhibitor-1), dysfunction of the endothelium, elevated levels of fibrinogen, and inflammation have been added to hyperlipidaemia, arterial hypertension, smoking, and diabetes mellitus[4-12].

Fibrinogen is a dissolvable glucoprotein with high molecular weight (MW), produced in the liver with a half living time of 86-100 hours and an acceptable mean serum level of less than 300 mg/dl. Its levels are influenced as much by genetic and hereditary factors as by acquired ones. High fibrinogen levels are considered to be very sensitive prognostic indexes for unstable forms of CAD (unstable angina, acute infarction)[4-9].

Tissue plasminogen activator (t-PA) and plasminogen activator inhibitor (PAI-1) contribute through plasmine to lysis or stabilization of haemorrhagic thrombus. Their values vary widely in venous thromboses, ischaemic heart disease, diabetes mellitus and obesity. The acceptable normal values for PAI-1 are between 4-43 ng/ml and for t-PA 1-12 ng/ml[4-6,8,13-14].

The presence of inflammation at the site of the atherosclerotic lesion plays an important role in the natural history of the endothelial injury. The participation of the macrophages and their excreted substances in the inflammatory process contributes to the rupture of unstable atheromatic plaques that are responsible for the development of acute ischaemic episodes. The activation of coagulation factors, as a result of rupture, and its combination with platelets and fibrinogen lead to thrombus formation and to total or subtotal arterial occlusion[10-19].

There is growing evidence of the independent prognostic importance of the elevated serum levels of C-reactive protein (CRP) in acute ischaemic episodes (normal values 0.05-0.25 mg/dl). High levels of CRP in apparently healthy people without or with atypical coronary symptoms may indicate an underlying endothelial inflammation accompanied by an accumulation of inflammatory cells (macrophages, smooth muscle cells, T-lemphocytes) in an unstable, relatively small, atheromatic coronary plaque which leads to its progressive activation and finally to rupture[10-12].

There is also strong evidence that hypolipidaemic drugs such as statins, in addition to their main action of reducing lipid levels, have a favorable influence upon clinical CAD manifestations, not only reversing the long term atherosclerotic process (2-2.5 years) but also directly improving the endothelial function, resulting in plaque stabilization and a reduction in the incidence of acute ischaemic episodes[10-24].

The aim of the study was to test the hypothesis that statins and healthy modified models of diet and way of living have a favorable influence upon the prognostic values of t-PA, PAI-1, fibrinogen, and CRP in hyperlipidaemic patients with angina.

Methods

We studied 206 hyperlipidaemic patients (phenotypes IIa and IIb, according to Fredricson) of both sexes (M=116, F=90, mean age 51.7+ 6.8 years) hospitalized in our department with angina manifestations. One hundred and fifty six patients (M=96, F=60) suffered from stable angina while the remaining 40 (M=20, F=20) suffered from unstable angina.

The above patients were divided into two groups. Group A consisted of 65 patients, 44 with stable angina (M=31, F=13) and 21 with unstable angina (M=12, F=9 0, treated with pravastatin 20 mg daily while Group B consisted of 141 patients, 112 with stable angina (M=62, F=60) and 29 with unstable angina (M=13, F=16), treated with fluvastatin 40 mg daily.

A detailed history and an ECG were obtained at baseline from all patients in order to clarify the clinical status of angina manifestations, stable or unstable. The criteria for definition of unstable angina were: a) prolonged retrosternal pain of greater than 30 min duration that appeared with minimal exercise and/or in rest without responding to sublingual nitrates; b) electrocardiographic changes (ST depression and/or T inversion); c) absence of pathological alterations in CpK-MB, SGOT, SGPT, LDH blood levels. All patients were estimated for fasting (12 hours of fasting), total cholesterol (total-ch), LDL-ch, HDL-ch, triglycerides, t-PA, PAI-1, fibrinogen, CRP blood glucose, CpK-MB, SGPT, SGOT, and LDH. Patients with acute myocardial infarction (AMI), arterial hypertension, diabetes mellitus, or who were taking drugs such as b-blockers, anticoagulation, non-steroids and had conditions affecting the acute inflammatory proteins were excluded from the study.

After the recruitment, the administration of any antilipidaemic drug was interrupted for two weeks and all patients followed the specific model of diet (hypolipidaemic diet, exercise, cessation of smoking, reduction in body weight) for the next three months together with the newly added antilipidaemic

therapy (pravastatin or fluvastatin) at the end of the first two weeks.

All patients with unstable angina at the end of the first month of follow-up underwent an exercise test (Ex).

At the end of the three-month period, all patients underwent the same clinical, biochemical and electrocardiographic estimations as at baseline.

Mild smokers (< 10 cigarettes daily) and obese patients were present in both groups in the same proportions.

The quantitative estimation of all parameters was carried out in our laboratory. The biochemical parameters were estimated using the chromatometric method and reagents provided by Randox, U.K. The fibrinogen serum levels were estimated using microlatex particle-mediated immunoassay (clotting method) and reagents provided by Diagnostica Stago, France. The CRP serum levels were estimated using the nephelometric method and reagents provided by Biosystems, Spain. PAI-1 and t-PA serum levels were estimated by an immunoassay method (Elisa) using reagents provided by Diagnostica Stago, France.

Statistical analysis was performed using the t-Students test with the biostatistical program Primer for Windows.

Results

The concurrent application of our healthy modified model of diet and living and antilipidaemic drug treatment for three months resulted in:

1) A statistically significant reduction of total-ch, triglycerides, LDL-ch levels and a significant elevation of LDL-ch (Table 1) compared to those at baseline.
2) A reduction of fibrinogen levels: 7.9% in fluvastatin group ($p<0.05$) and 4.8% in pravastatin group (Table 2).
3) A statistically significant reduction of PAI-1 levels and a statistically significant elevation of t-PA levels compared to those at baseline (Table 2).
4) A statistically significant elevation ($p<0.001$) of CRP levels at baseline in patients with unstable angina compared to those with stable angina and with normal values (Table 3).
5) A greater reduction ($p<0.05$) of CRP levels after three months' treatment with pravastatin compared to those with fluvastatin (Table 3).
6) A good long-term outcome for all patients. Thirty-two patients from the group with unstable angina had a positive for CAD exercise test (Ex) performed one month after discharge whilst the remaining 8 had an uncertain or negative Ex. Twenty four of them underwent coronary angiography with stenotic lesions < 50% in one or two arteries. Drug treatment was continued and an appointment after six months was recommended.
7) A non-statistically significant elevation within normal levels of SGPT, SGOT, CpK-MB. The levels of serum glucose and the other biochemical parameters were not influenced.

Table 1. Alterations in lipid levels

	Initial values	p^*	Pravastatin	p^{**}	Fluvastatin	p^*
Total-ch (mg/dl)	311.0±35.0	0.001	228.4±28.1	NS	222.7±31.0	0.001 *
Triglycerides (mg/dl)	210.0±24.0	0.001	155.6±23.5	NS	147.6±21.9	0.001 *
HDL-ch (mg/ml)	36.8±12.7	0.001	39.4±10.1	NS	40.0±11.1	0.001 *
LDL-ch (mg/dl)	232.0±16.8	0.001	157.9±18.2	NS	156.7±19.0	0.001 *

p^* = compared to initial values, p = between two groups (pravastatin and fluvastatin).

Table 2. Alterations in fibrinogen, PAI-1 and t-PA levels

	Initial values	p^*	Pravastatin	p^{**}	Fluvastatin	p^*
Fibrinogen (mg/dl)	406.0±44.0	0.05	398.0±47.0	0.05	373.9±37.8	0.001
PAI-1 (ng/dl)	39.4±11.2	0.001	34.8±9.2	NS	33.4±9.8	0.001
t-PA (ng/dl)	8.1±2.9	0.001	10.2±2.4	NS	10.7±2.8	0.001

p^* = compared to initial values, p^{**} = between the two groups (fluvastatin and pravastatin).

Table 3. Alterations in CRP (mg/dl) values

Angina	Initial values	p**	Pravastatin	p***	Fluvastatin	p**
Stable	0.10±0.002 *	NS	0.095±0.002	NS	0.098±0.002	0.05
Unstable	0.30±0004 *	0.001	0.19±0.001	0.05	0.24±0.001	0.05

p* < 0.001 between the groups with stable and unstable angina at baseline,
p** = compared to initial values,
p*** = between the two groups (fluvastatin and pravastatin).

8) Gastroenteritis in six patients which was managed without interrupting administration of the antilipidaemic drug.

Discussion

Hyperlipidaemia has been documented by numerous well organized clinical and epidemiological studies (4S [25], WOS [26], CARE [27], FLINT [28], LCAS [29], FLARE [30], LIPID [31]) as the major CAD risk factor. The hypothesis that the reversion of atheromatic lesions is possible when long-term (2-2.5 years) hypolipidaemic drug treatment results in a reduction of total and LDL serum cholesterol, has also been supported by these studies[25-30].

The appearance of a thrombus superimposed on the erosion or fissure of an atherosclerotic plaque is the mechanism involved in the sudden development of acute ischaemic episodes. According to a newly developed concept, the levels of lipids, fibrinogen, PAI-1, t-PA and the presence of inflammation and endothelial dysfunction at the site of the lesion (macrophages, smooth muscle cells, T-lemphocytes, cytokines, interleukines etc.) gradually activate the unstable, relatively small, atheromatic coronary plaques resulting in their rupture and activation of thrombogenic factors that finally lead to formation of a thrombus responsible for total or subtotal occlusion of the artery involved[6-14].

Statins are a relatively new, effective type of antilipidaemic drug with well studied action mechanisms and few reversible side effects. Pravastatin is a natural first generation hydrophilic statin while fluvastatin is the first synthetic hydrophilic statin[15-18].

The ability of hydrophilic statins to delay or to reverse the atheromatic process and the underlying mechanisms (fibrinogen t-PA, PAI-1, macrophages, pre-inflammatory cytokines) has been the subject of extensive research[10-24]. The multiple capabilities of statins seem to improve the overall endothelial function resulting, in a long-term reduction of acute ischaemic episodes[10-24, 32-36].

Analyzing our findings, the administration of pravastatin (20 mg/daily) and fluvastatin (40 mg/daily) in conduction with a healthy modified model of diet and exercise for a period of three months has resulted in to:

1. A statistically significant improvement in lipid levels in both groups of patients (pravastatin or fluvastatin) compared to those at baseline; no significant differences were observed between the abilities of the two drugs to reduce the lipid levels (Table 1). These results are close to other reports and underline the equally effective antilipidaemic action of pravastatin and fluvastatin on lipidaemic profile12-19, 25-31.

2. A reduction of fibrinogen levels (7.9%) by fluvastatin with statistical significance compared to those at baseline ($p<0.001$) while pravastatin resulted in a smaller reduction (4.8%) compared to initial values ($p<0.05$) (Table 2). In addition, the administration of both statins seems to have an equal effect in improving with statistical significance ($p<0.001$) the fibrinolytic mechanism (PAI-1 reduction and t-PA elevation) compared to initial values (Table 2). These findings support other studies that indicate the favorable action of hydrophilic statins on thrombogenic factors10-19, 32-36 and the fibrinolytic system15-21, 32-33.

3. A statistically significant reduction of CRP levels (patients with unstable angina) by pravastatin ($p<0.001$) compared to those at baseline, while fluvastatin resulted in a less significant reduction ($p<0.05$) (Table 3). The CRP levels were at baseline significantly elevated ($p<0.001$) in the patients with unstable angina compared to normal values and to those of patients with stable angina (Table 3). These findings support other reports that indicate the favorable influence of both statins on the inflammatory process[10-14, 34-44].

The good long-term outcome of these patients and the low incidence of side effects in combination with the favorable action on the inflammatory process and thrombogenic and fibrinolytic mechanisms underline the efficiency of these hydrophilic statins

and improve the prognostic evaluation of hyperlipidaemic coronary patients[4-8,13,21,28,29].

The combination of a hypolipidaemic diet, regular exercise, cessation of smoking, loss of body weight and hydrophilic statins seems to act favorably in hyperlipidaemic coronary patients, improving clinical status and anatomic lesions. This action is achieved by functionally improving the endothelium, suppressing the inflammation, reducing the thrombogenesis, supporting the fibrinolysis and decreasing the lipid levels.

Our conclusions indicate the need for more extensive and longer lasting studies that may provide definitive proof of the action of statins on the underlying mechanisms responsible for the atherosclerotic process.

Περίληψη

Ευθυμιάδης Απ, Ψυρρόπουλος Δ, Ευθυμιάδης Ι, Λευκός Ν. **Επίδραση των στατινών στα λιπίδια, στο ινωδογόνο και στις παραμέτρους φλεγμονής ατόμων με αυξημένο κίνδυνο στεφανιαίας νόσου.** Ιπποκράτεια 2002, 6: 4: 186-192

Σκοπός της εργασίας είναι ο έλεγχος των μεταβολών των λιπιδίων, των παραγόντων πήξης-ινωδόλυσης (ινωδογόνου, PAI-1, t-PA) και των παραμέτρων φλεγμονής (CRP), με την εφαρμογή ειδικού υγιεινοδιαιτητικού προγράμματος και τη σύγχρονη χορήγηση στατίνης, σε υπερλιπιδαιμικά άτομα με στηθάγχη.

Μελετήθηκαν συνολικά 206 ασθενείς και των δύο φύλων (Α=116, Γ=90, μέσης ηλικίας 51,7+6,8 έτη). Την ομάδα Α αποτέλεσαν 65 ασθενείς, 44 με σταθερή στηθάγχη (Α=31, Γ=13) και 21 με ασταθή στηθάγχη (Α=12, Γ=9) που έπαιρναν αγωγή με πραβαστατίνη 20 mg/ημ. ενώ την ομάδα Β αποτέλεσαν 141 ασθενείς, 112 με σταθερή στηθάγχη (Α=62, Γ=60) και 21 με ασταθή στηθάγχη (Α=13, Γ=16) που έπαιρναν αγωγή με φλουβαστατίνη 40 mg/ημ. Όλοι έπασχαν από πρωτοπαθή υπερλιπιδαιμία (φαινότυποι ΙΙα και ΙΙβ κατά Fredricson. Ανάλογος αριθμός ατόμων και στις δύο ομάδες ήταν μέτριοι καπνιστές (<10 τσιγάρα ημ.) και υπέρβαροι, ενώ κανένα δεν ανέφερε ιστορικό αρτηριακής υπέρτασης ή σακχαρώδη διαβήτη. Όλα τα άτομα τέθηκαν σε ειδική υγιεινοδιαιτητική αγωγή, όπως υπολιπιδαιμική δίαιτα, διακοπή του καπνίσματος και εφαρμογή ειδικού προγράμματος ασκήσεων, με σύγχρονη υπολιπιδαιμική φαρμακευτική αγωγή, για χρονικό διάστημα παρακολούθησης τριών μηνών, οπότε έγινε νέος βιοχημικός προσδιορισμός (σάκχαρο, χοληστερίνη, τριγλυκερίδια, HDL-χ LDL-χ , τρανσαμινάσες, ινωδογόνο, PAI-1, t-PA και CRP) και κλινική και ΗΚΓ/κή επανεκτίμηση.

Η εφαρμογή υγιεινοδιαιτητικής αγωγής με τη σύγχρονη προσθήκη του δραστικού φαρμάκου (πραβαστατίνης ή φλουβαστατίνης) για τρεις μήνες: 1. μείωσε στατιστικά σημαντικά, σε σχέση με τις αρχικές, χωρίς σημαντικές διαφορές μεταξύ των δύο φαρμάκων, τις τιμές της ολικής χοληστερόλης, των τριγλυκεριδίων και της LDL-χ ενώ αύξησε την τιμή της HDL-χ. 2. Οι τιμές του ινωδογόνου μειώθηκαν κατά 7,9% με τη φλουβαστατίνη και 4,8% με την πραβαστατίνη, ενώ μειώθηκαν στατιστικά σημαντικά οι τιμές του PAI-1 και αυξήθηκαν οι τιμές του t-PA, χωρίς η διαφορά μεταξύ των φαρμάκων να είναι σημαντική. 3. Οι τιμές της CRP βρέθηκαν σημαντικά αυξημένες στους ασθενείς με ασταθή, σε σχέση με την ομάδα με σταθερή στηθάγχη και τις φυσιολογικές τιμές της μεθόδου. 4. Η χορήγηση της πραβαστατίνης προκάλεσε μεγαλύτερη μείωση των τιμών CRP, συγκριτικά με τη φλουβαστατίνη. 5. Οι παρενέργειες από τη λήψη των φαρμάκων, κλινικές και βιοχημικές δεν ήταν αξιόλογες, ικανές να καταστήσουν απαραίτητη τη διακοπή τους.

Ο συνδυασμός υγιεινοδιαιτητικού προγράμματος με τη σύγχρονη χορήγηση πραβαστατίνης ή φλουβαστατίνης για τρεις μήνες, βρέθηκε ότι βελτιώνει σημαντικά τις τιμές των λιπιδίων, ασκεί ευεργετική επίδραση στις τιμές του ινωδογόνου, τους παράγοντες πήξης-ινωδόλυσης και φλεγμονής (CRP) ατόμων με πρωτοπαθή υπερλιπιδαιμία και στεφανιαία νόσο, συμβάλλοντας στην καλύτερη λειτουργικότητα του ενδοθηλίου, με συνέπεια, λόγω της ανασταλτικής αθηρογενετικής και θρομβογενετικής δράσης, μείωση των συνεπειών της αθηροσκληρωτικής εξεργασίας και του κινδύνου οξέος στεφανιαίου επεισοδίου από τη ρήξη της αθηρωματικής πλάκας.

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