

4 Statin-Induced myotoxicity: An overview of the risk factors

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Grants: This work has been supported by the Aristotle University Research Committee and the Hellenic Harvard Foundation.

Announcement: We would like to thanks Dr Tsiamis Nikolaos for the contribution in editing of this paper.

ABSTRACT: Statins are well tolerated and particularly safe medicines. The most important clinical side effect of statins is myotoxicity. Rhabdomyolysis is the most rare, but most serious of myotoxicity. Clinically it is characterized by proximal or diffuse muscle pain, weakness and myoglobinuria. CPK usually exceeds by far 10 times the upper limit of normal.

Factors, which increase the risk of myotoxicity, are: advanced age and female gender (for unknown reasons), genetic polymorphism (low hepatic or intestinal expression of the isoenzyme CYP3A4), hereditary myopathy, lipophilicity of some statins, high doses of statins (dose-dependent side effect), medicines and foods that are metabolized by CYP3A4, renal failure and hepatic dysfunction, as well as the conditions that worsen them.

Key Words: Myotoxicity, Statins, CYP or P450 Cytochrome.

I. INTRODUCTION

Atherosclerotic cardiovascular disease constitutes the most frequent cause of morbidity and mortality in developed countries. Since one of the key risk factors of atherosclerosis is dyslipidemia, the decrease of LDL cholesterol levels through diet and/or hypolipidemic medicines slows the progress of atherosclerosis, thus decreases the probability of cardiovascular incidents^{1,2}. Among hypolipidemic medicines, statins represent the most effective and most commonly administered ones³.

Statins are competitive inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the enzyme that is found on the membrane of the endoplasmic reticulum and catalyzes the conversion of HMG-CoA into mevalonic acid^{4,5}. By doing so in the hepatocytes, the biosynthesis and thus

the accumulation of cholesterol in the cytoplasm of the latter fall. This results in an upregulation of LDL receptors on the surface of hepatic cells and consequently in an increase of LDL catabolism.

Statins are well tolerated and particularly safe medicines as shown by the results of extensive clinical research^{4,5,8,9,10,11}. Their side effects are usually mild and reversible and are seldom observed. The most important clinical side effect is myotoxicity, which is dose-dependent, is associated with all statins (class effect) and usually develops within the first three months of treatment^{1,4,5,12} although rhabdomyolysis can occur at any time a person is taking a statin. The clinical spectrum of myotoxicity includes: asymptomatic increase of CPK, myalgia, myopathy, rhabdomyolysis (Table 1)¹². The asymptomatic increase of CPK is a quite common finding. It consists of slight and

Table 1. The clinical spectrum of statin-induced myotoxicity.

| Clinical manifestation | Frequency | Symptoms | CPK | Histological findings |
|-------------------------------------|-----------------------------|--|-----------------------------|------------------------------------|
| Asymptomatic increase of CPK | Quite common finding | Without symptoms | Mild and temporary | No |
| Myalgia | Common finding | Proximal or diffuse muscle pain | Normal or slightly elevated | No |
| Myopathy | Rare finding | Proximal or diffuse muscle pain, weakness | >1000 U/l | Muscle fibres necrosis and rupture |
| Rhabdomyolysis | Rare, but potentially fatal | Proximal or diffuse muscle pain, weakness, myoglobinuria | Very elevated | Muscle fibres necrosis |

temporary rise of CPK, without symptoms and other laboratory findings. Myalgia is a frequent finding and is characterized by proximal or diffuse muscle pain and weakness. CPK is normal or slightly increased, without histological findings of myopathy. Myopathy is characterized by proximal or diffuse muscle pain and weakness, accompanied by increase of CPK above 10 times the upper limit of normal (1000 U/l). Pathologically, necrosis and rupture of muscle fibres are observed. Rhabdomyolysis is the most rare, but most serious side-effect. It is the acute, deteriorating, potentially fatal rupture of muscle fibres accompanied by the release of CPK, myoglobin and other intracellular substances into the serum. Clinically it is characterized by proximal or diffuse muscle pain, weakness and myoglobinuria. CPK usually exceeds by far 10 times the upper limit of normal. Pathologically necrosis of muscle fibres is observed.

When prescribing statins, there is a small inherent risk of myotoxicity. When certain factors co-exist, then this risk is increased. For the better understanding of those factors, it is essential to know the physicochemical and pharmacokinetic properties of statins.

II. Physicochemical properties of statins

Lovastatin is the first statin that was approved in 1987, followed by simvastatin and pravastatin. Lovastatin and pravastatin are produced by fungus fermentation while simvastatin is semisynthetic^{1,2,4,12}.

Lovastatin and simvastatin are administered as inactive lactones and through first-pass metabolism at the P450 cytochrome enzymatic system they are hydrolyzed into beta hydroxy acids, which constitute the active metabolites. Pravastatin is administered in its active form. Lovastatin and simvastatin are lipophilic and they pass through the blood brain barrier, while pravastatin is hydrophilic and does not. Fluvastatin is a second generation statin, while recently third generation statins atorvastatin and cerivastatin* have emerged^{1,2,4,12}. All three are entirely synthetic and are administered in their active form. Moreover, atorvastatin and cerivastatin give active metabolites through hepatic first pass metabolism. Regarding their water solubility, fluvastatin has an intermediate status, while atorvastatin and cerivastatin are lipophilic. Apart from cerivastatin, the other two do not cross the blood brain barrier. Rosuvastatin is the most recently approved statin, whereas pravastatin has not reached this point yet¹³. The physicochemical properties of statins are shown in detail in Table 2.

III. CYP or P450 cytochrome system

Before going through the pharmacokinetic differences of various statins, we will cite useful facts concerning the operation of CYP or P450 cytochrome system. The cytochrome system CYP is the fundamental system of biotransformation of various exogenous (medicines, alcohol, toxic substances etc) and endogenous (steroids, bile acids, fatty acids, prostaglandins

* *Cerivastatin has been withdrawn from the market.*

Table 2. Physicochemical and pharmacokinetic properties of statins.

| Characteristic | Lovastatin | Simvastatin | Pravastatin | Fluvastatin | Atorvastatin | Cerivastatin | Rosuvastatin |
|-------------------------------------|----------------------|---------------|----------------------|--------------|--------------|----------------|----------------|
| Daily dose (mg) | 20-80 | 10-40 | 10-40 | 20-80 | 10-80 | 0.1-0.3 | 10-40 |
| Origin | Fungi | Semisynthetic | Fungi | Synthetic | Synthetic | Synthetic | Synthetic |
| Prodrug | Yes | Yes | No | No | No | No | No |
| Solubility | Lipophilic | Lipophilic | Hydrophilic | Intremediate | Lipophilic | Lipophilic | Hydrophilic |
| CNS permeation | Yes | Yes | No | No | No | No | No |
| Effect of food intake on absorption | Increased absorption | None | Decreased absorption | None | None | None | None |
| Optimal time of dosing | Morning and evening | Evening | Before sleep | Before sleep | Evening | Evening | Any |
| First pass metabolism | CYP3A4 | CYP3A4 | Multiple ways | CYP2C9 | CYP3A4 | CYP3A4, CYP2C8 | Limited CYP2C9 |
| Bioavailability (%) | <20 | <5 | 18 | 25 | 12 | 60 | 20 |
| Protein binding (%) | 95 | 95 | 50 | 98 | 98 | >99 | 88 |
| Half life (hours) | 2-3 | 2-3 | 1-2 | 0.5 | 13-16 | 2-3 | 19 |
| Hepatic extraction (%) | 69 | 79 | 46 | >68 | NAD | 20-25 | 63 |
| Renal Excretion (%) | 30 | 13 | 60 | <6 | <2 | 24 | 10 |

NAD= No Available Data

etc) substances^{14,15,16,17,18}. The CYP cytochromes are hemoproteins that are found in the membrane of the smooth endoplasmic reticulum of hepatic cells mainly, but also in smaller quantities in cells of other tissues (small intestine, kidneys, brain, lungs etc)^{19,20}. Concerning their name P450, P stands for the word pigment and 450 represents the wavelength in nm of maximal photometric absorption of the reaction products of P450 with CO¹⁸. Their main function is the biotransformation (acidosis, hydroxylation, hydrolysis, dealkylation, demethylation, reduction) of different substances into more water-soluble molecules, so that they can be more easily excreted from the body¹⁸. When the CYP or P450 cytochromes pres-

ent at least 40% sequence homology regarding their primary structure, they are then classified in the same family²¹. The cytochrome families are denoted with arabic numbers for example CYP1, CYP2, CYP3. Each family is divided in subfamilies that are given a capital Latin letter e.g. CYP2C, CYP2D, CYP3A. The members of each subfamily have more than 55% sequence homology. Finally, each enzyme of every subfamily is distinguished by other isoenzymes with an arabic number e.g. CYP3A4. In humans 14 families and 20 subfamilies of cytochromes exist¹⁸. The majority of all clinically important medicines are metabolized by families CYP1, CYP2, CYP3 that compose 70% of hepatic P450 cytochromes²². CYP3A4

is the most common isoenzyme in the hepatic cells (approximately 30% of hepatic cytochromes) and is in charge of the metabolism of about 50% of medicines and endogenous steroids^{19,23}. Apart from the liver, it is found in significant concentrations in the epithelial cells of small intestine (approximately 70% of intestinal cytochromes). Also important is the subfamily CYP2C that constitutes 20% of liver's P450 cytochromes²³. Its main representative is the isoenzyme CYP2C9. Given that the substrate specificities for many isoenzymes in the CYP2C subfamily overlap, it is relatively rare to observe intense side-effects when the above isoenzymes are involved²³.

IV. Pharmacokinetic properties of statins^{1,2,12,24}

As it is shown in Table 2, the absorption of statins is not influenced by the consumption of food, with the exception of lovastatin, the absorption of which is increased when taken with food, and pravastatin, where the opposite happens. The optimal time for administering statins is the afternoon or evening hours because the HMG CoA reductase follows circadian rhythm and presents increased activity at these hours.

The first pass metabolism takes place mainly in the small intestine's mucosa and in the liver by the CYP cytochrome system. Lovastatin, simvastatin, atorvastatin and cerivastatin are metabolized by the CYP3A4 cytochrome. Administering the abovementioned statins with medicines and foods that, either inhibit (cyclosporine, macrolide antibiotics, azole antifungals, grape-fruit juice etc), or are substrates of CYP3A4, decreases the first pass metabolism of statins resulting in the increase of their serum bioavailability. Cerivastatin has an additional alternative metabolic pathway via CYP2C8 cytochrome, that theoretically appears to decrease the probability of serious unwanted pharmacokinetic interactions with CYP3A4 inhibitors^{2,12,24,25,26,27,28,29,30}. Fluvastatin is metabolized mainly by CYP2C9 and consequently does not interact with medicines that inhibit CYP3A4^{2,12,23,24,31,32}. The interactions with CYP2C9 inhibitors and substrates are relatively mild and this is probably attributed to the fact that subfamily CYP2C has the advantage of overlapping substrates specificity, that is to say a substrate can be metabolized by different isoenzymes of the same subfamily. Finally,

water-soluble pravastatin is metabolized to a small extent (1%) from CYP cytochromes and is excreted unchanged through the urine and feces^{2,12,33,34}. This makes it safer, as far as its metabolism is concerned, in comparison to the previous four statins.

The systematic bioavailability of statins is quite low (25%) with the exception of cerivastatin (60%). All statins present a high affinity with blood proteins (95%), except pravastatin (roughly 50%). The half life is on average 1-3 hours. Atorvastatin is the only statin that has longer half life (13-16 hours) as well as rosuvastatin and this property is most probably linked to their higher efficacy. With regard to their excretion, this is done mainly via the liver and to a lesser extent via the kidneys. Pravastatin is the only one that is removed to a significant extent by the kidneys (around 60% of the absorbed quantity) in keeping with its hydrophilic nature.

V. Risk factors of statin-induced myotoxicity

When administering statins, the physician must take into consideration a series of factors, which increase the risk of myotoxicity.

1. Patient characteristics

It has been observed epidemiologically that advanced age and female gender (for unknown reasons) are two factors that increase the myotoxic effect of statins^{4,35,36}. Another important factor is the pharmacokinetic differences attributable to genetic polymorphism^{12,37,38,39}. More specifically, it has been observed that there is considerable variation in the concentration and activity of the isoenzyme CYP3A4 both in the liver and in the small intestine. The same applies to all CYP cytochromes. Given that lovastatin, simvastatin, atorvastatin and cerivastatin are metabolized by CYP3A4 enzymes, low hepatic or intestinal expression of this isoenzyme (poor metabolizer) leads to decreased first pass metabolism for the aforementioned statins, increasing the danger of myotoxicity and the other way round. The prevalence of rhabdomyolysis may be higher in patients with existing hereditary myopathy^{40,41}. In that case, the administration of statins is not absolutely contraindicated; however close clinical and laboratory control of patient's muscular function is necessary.

Table 3. Substances that increase the myotoxic potential of statins.

| Non hypolipidemic medicines |
|--|
| Cyclosporine |
| Macrolide antibiotics (erythromycin, clarithromycin) |
| Azole antifungals (itraconazole, ketoconazole, fluconazole) |
| Calcium channel blockers (mibefradil*, diltiazem) |
| Nefazodone |
| HIV protease inhibitors (ritonavir, nelfinavir, indinavir) |
| Warfarin |
| H ₂ antagonists (cimetidine, ranitidine) |
| Omeprazole |
| Hypolipidemic medicines |
| Fibrates (gemfibrozil, bezafibrate, clofibrate, fenofibrate) |
| Nicotinic acid |
| Bile acids resins (cholestyramine, colestipol) |
| Other Substances |
| Grapefruit juice |

*Due to toxic interactions with other medicines it has been withdrawn from the market.

2. Physicochemical properties of statins

It has been acknowledged that all statins, either taken as monotherapy or in combination with other medicines, can cause rhabdomyolysis (class effect)¹². According to research data, pravastatin is the least myotoxic in relation to lovastatin and simvastatin^{42,43,44}. Masters et al⁴² studied the effect of various concentrations of lovastatin, simvastatin and pravastatin on the survival and the cholesterol-synthesizing capacity of neonatal rat skeletal muscle and hepatic cells. From the study it came out that, while the inhibition of cholesterol synthesis in hepatic cells was similar for the three statins, in the muscle cells the effect of pravastatin was 85 times weaker. Moreover, pravastatin was 100-200 times (in an inversely dose dependent mode) less myotoxic compared to lovastatin and simvastatin. This shows that different statins have diverse dose-dependent effects in the skeletal muscle fibers. The decreased myotoxicity of pravastatin appears to be related with its decreased uptake by extra-hepatic tissues. It is believed that pravastatin is taken up by the hepatic cells via a sodium-independent bile acid

transporter the Organic Anion Transporting Polypeptide (OATP)^{42,45,46,47}. The latter transporter along with sodium dependent taurocholate cotransporting polypeptide (NTCP) mediate the active hepatic uptake of the hydrophilic rosuvastatin. The lipophilic membranes of non-hepatic cells, such as muscle cells, lack OATP so that they function as a barrier to hydrophilic pravastatin, while they allow entry to lipophilic statins. In similar studies the importance of lipophilicity of statins in their myotoxic potential is also supported^{43,48}.

3. Dose dependent effects

Myopathy caused by statins is a dose-dependent side effect^{4,12,44,49}. For this reason it is recommended that the hypolipidemic treatment with statins begin with low doses that should be increased progressively and cautiously.

4. Drug interaction

The interaction of statins with other categories of medicines has either a pharmacokinetic basis, such

as during their concomitant administration with CYP cytochrome inhibitors, or a pharmacodynamic one, when statins are combined with agents which have an independent myotoxic effect like fibrates, where a pharmacokinetic component may also come into play.

A. Pharmacokinetic interactions with CYP inhibitors and substrates

a. Cyclosporine: Statins are the most effective medicines for the treatment of hypercholesteremia in patients that underwent transplantation^{50,51,52}. Besides, it appears that with their immunosuppressive action they provide general protection to the graft⁵². Because, however, cyclosporine inhibits CYP3A4 cytochrome activity, both in the liver and the small intestine, it can lead to increased bioavailability of statins that are metabolized by this cytochrome (lovastatin, simvastatin, atorvastatin, cerivastatin) (Table 3). The more lipophilic the statin and the greater the systemic exposure to unbound active statin compound, the greater the potential for myotoxic effects^{2,12,51,53,54,55,56,57}. On the contrary, pravastatin that is not metabolized considerably by CYP enzymes and fluvastatin that is metabolized by CYP2C9 cytochrome are less likely to interact with cyclosporine on a pharmacokinetic basis^{2,12,50,58}. As indicated by the World Health Organization's International Drug Information System, (WHO's INTDIS), most reports of rhabdomyolysis due to interaction of a statin with cyclosporine concern lovastatin and simvastatin^{12,50}. According to Tobert et al⁵⁹, the prevalence of myopathy of the lovastatin - cyclosporine combination can reach 30%. Even if the combination of lovastatin or simvastatin with cyclosporine is not contraindicated and in fact may be even indicated because of pleiotropic immunomodulatory effects of the statins and importantly because of cyclosporine's adverse effects on the lipid profile, it should be administered with high caution and under strict clinical and laboratory control⁶⁰. Although the clinical reports are limited for the newest statins, atorvastatin and cerivastatin, their pharmacokinetic properties render likely such an interaction, and for this they should be administered with caution and in small doses^{61,62}. Consequently, in patients that have undergone transplantation and are taking cyclosporine it is recommended to adminis-

ter pravastatin or fluvastatin^{50,58,63}. In any case, small doses of statins must be given, the patient will have to be advised for the probability of myopathy and it will be necessary to check for muscle side effects, at least during the first months of treatment.

b. Other inhibitors of CYP3A4: Apart from cyclosporine, there are other inhibitors of CYP3A4 enzyme, which, when they are combined with statins, decrease the first pass metabolism of statins and increase statins' levels in serum and the probability of myotoxic effects. The main such enzymatic inhibitors are azole antifungals (itraconazole, ketoconazole, fluconazole)^{2,12,64,65,66,67,68,69,70,71,72}, macrolide antibiotics (erythromycin, clarithromycin)^{2,12,58,68,73,74,75}, calcium channel blockers^{2,74}, antidepressant nefazodone^{2,12,76}, HIV protease inhibitors (ritonavir, nelfinavir, indinavir)^{2,4} and grapefruit juice^{2,77,78,79} (Table 3). Among statins, lovastatin, simvastatin, atorvastatin and cerivastatin that are metabolized by CYP3A4 appear to have the highest myotoxic potential when combined with the abovementioned substances^{12,33,58,80,81}. For this reason it is considered advisable to avoid such type of combinations, either by temporary suspension of statins or by administering alternative treatments⁶⁷. If such a combination is deemed necessary, it will be essential to give small doses of statins, advice the patient about the probability of myopathy, and regular clinical and laboratory follow-up for muscular side effects must take place. On the contrary, pravastatin and fluvastatin are not metabolized to a significant extent by CYP3A4 and so they interact less with the aforementioned medicines, constituting safe alternatives^{12,33,58,65,66,80,81,82}.

c. Warfarin: There have been reported incidents of rhabdomyolysis during the co-administration of statins with warfarin^{12,82,83}. The combination of statins with warfarin is likely to increase the serum levels of warfarin resulting in the prolongation of prothrombin time (PT). For this reason regular measurement of PT is required⁸⁴. On the contrary, the effect of warfarin on the levels of statins has not been studied sufficiently. A hypothesis has been articulated that as warfarin constitutes substrate of CYP2C9, and partly of CYP3A4, it could compete with statins in their enzymatic conversion from those cytochromes and increase their levels in serum⁸². Since a great percent-

age of patients with cardiovascular disease receives simultaneously statins and warfarin and until new data come along, it is deemed advisable to administer small doses of statins and have the patient under careful clinical and laboratory follow-up for the possibility of myopathy.

d. H₂ antagonists and proton pump inhibitors:

The co-administration of fluvastatin with cimetidine, ranitidine and omeprazole, which are enzymatic substrates of CYP2C9, increases fluvastatin's bioavailability, without however particular clinical significance. As mentioned before, this is probably attributed to the fact that the isoenzymes of the CYP2C family present overlapping substrates specificity.

B. Interactions with other hypolipidemic medicines

a. Fibrates: In many cases of mixed dyslipidemia, statins are co-administered with fibrates. According to international data, the combination of any statin with fibrates increases the danger of myotoxicity (class effect), that is usually observed within the first 12 weeks by the initiation of treatment⁸⁵. Even if most reports involve gemfibrozil^{2,12,35,36,51,85,86,87,88,89,90,91,92,93,94}, the other fibrates (bezafibrate, clofibrate, fenofibrate) cannot be considered absolutely safe^{12,36,95}. In the international bibliography there have been 29 reported cases of rhabdomyolysis from co-administration of a statin (21 were given lovastatin, 4 simvastatin, 3 cerivastatin and 1 atorvastatin) and a fibrate (in all cases gemfibrozil)⁸⁵. None of these cases was fatal. 66% developed acute renal failure and 6 of them needed dialysis. The presence of gemfibrozil in all cases of rhabdomyolysis is explained, partly, from its wider clinical use compared to other fibrates. Moreover, in WHO's INTDIS database there are cases of rhabdomyolysis attributed to combination of statin with bezafibrate and fenofibrate¹². Regarding the incidence of myotoxicity when statins are combined with a fibrate, according to recent studies, it amounts to 1-2%^{85,88}. Since fibrates are not inhibitors of CYP cytochromes, the myotoxic effect when combined with statins appears to have a pharmacodynamic basis (synergy) and to relate to fibrates' myotoxic potential when given independently^{25,35}. Accordingly, the co-administration of statins with fibrates must be done cautiously and only after it is ascertained that the expected benefit outweighs possible risks³⁵. Particular

attention is required for patients with increased levels of transaminases and CPK, renal failure, hepatic dysfunction and myopathy^{2,36,96,97}. In case of administration of a combination, small doses must be given, CPK must be regularly measured, the patient must be accurately informed and under clinical surveillance for muscular symptoms such as myalgia, muscle tenderness and weakness. Although the interaction of statins with fibrates is a class effect, it appears that pravastatin⁹⁰ and fluvastatin^{98,99} are relatively safe. It has been proposed that in high risk patients with mixed dyslipidemia, a fibrate with short half life can be administered in the morning and a small dose of hydrophilic statin with short half life e.g. pravastatin in the afternoon^{25,35}. However the safety of this combination has not yet been proved.

b. Nicotinic acid (niacin): The concomitant administration of statins with high doses of nicotinic acid can lead to rhabdomyolysis through a mechanism that remains unknown, but does not appear to be related to the increase of serum concentration of statins^{2,12,59,99, 100,101,102}. This interaction pertains to all statins. In clinical studies approximately 2% of patients that were taking lovastatin and nicotinic acid at the same time developed myopathy⁵⁹. In order to make the combination of statins with nicotinic acid safer it is recommended to administer low doses, to brief the patients on the possibility of myopathy, to regularly measure CPK and to watch closely for possible muscle symptomatology⁹⁹.

c. Resins of bile acids: Very few incidents of rhabdomyolysis have been reported when statins were combined with cholestyramine^{2,12,103,104} and colestipol². Although the mechanism of interaction remains unidentified, physicians ought to take this into consideration.

5. Other risk factors

The administration of statins should be done with great caution and, if it is possible to be avoided or to be interrupted temporarily, in cases of renal failure^{4,12}, hepatic dysfunction^{4,12}, chronic consumption of alcohol and drugs (amphetamines, cocaine, heroin, LSD, ecstasy etc.)¹², hypothyroidism and other endocrine disorders^{4,105,106}, serious viral (Influenza A and B, EBV, CMV, HSV, HIV, Coxsackie etc.) or bacterial (Streptococcus, Staphylococcus, Legionella,

Leptospira, E.Coli, Salmonella etc.) infection¹², extensive surgical operations, major trauma¹², epileptic seizure¹², hypothermia¹², hypoxia¹², hypotension, electrolyte imbalance⁵, metabolic acidosis¹⁰⁷, intense muscle activity¹² etc.

VI. Recommendations for prevention of muscle side-effects during the co-administration of statins with other medicines

Given the continuously increasing use of statins to treat dyslipidemia, their co-administration with other medicines is frequently inevitable. Since many such combinations are potentially myotoxic, it is essential to have some guidelines in order to avoid this risk²:

- The doctor must be familiar with the pharmacokinetic and pharmacodynamic properties of each statin, in order to be able to predict and to deter its interaction with other medicines. It is advisable, after the benefit is weighed against the risk, whenever possible, to avoid the co-administration of statins with fibrates, nicotinic acid, cyclosporine, azoles, macrolides, HIV protease inhibitors, nefazodone, grape-fruit juice etc. This can be achieved either by temporary suspension of statins, or by opting for alternative therapeutic options. In case where the administration of a combination is deemed necessary, for instance in transplanted patients with hypercholesterolemia, it is better to choose the safest statins⁸¹.
- Before the initiation of treatment the levels of CPK must be checked. If the levels of CPK are above three times the upper limit of normal, then it is wise to avoid statins.
- Small doses of statins should be given at the beginning of the treatment
- If it is required to co-administer a statin with a fibrate, it is recommended to administer a fibrate with small half-life in the morning and a small dose of a hydrophilic statin with small half-life in the afternoon.
- Patients should be advised to report immediately to their doctor any unexplained muscle pain, tenderness or weakness, particularly if it is accompanied by fever or malaise.
- Regular clinical follow-up of patients for muscle symptoms and signs, especially during the first months of treatment.
- Regular checks of CPK, particularly when statins are co-administered with fibrates. Without any concrete guidelines existing, some propose check of CPK 6 and 12 weeks after the beginning of treatment and subsequently every three months for the first year and every 6 months or annually after the first year. If clinical manifestations of myopathy (even without increase of CPK) or asymptomatic increase of CPK above three times the upper limit of normal is observed, it is recommended to interrupt the hypolipidemic treatment. In case the patient is asymptomatic and the CPK is lower than three times the upper limit of normal, then it is recommended to repeat the tests after 2 weeks. If an augmentative tendency of CPK is observed, then it is advisable to suspend the hypolipidemic medicines.
- When acute pathological or surgical conditions that can precipitate rhabdomyolysis co-exist (renal failure, hepatic dysfunction, serious acute infection, hypotension, serious electrolyte, metabolic and endocrine disorders, uncontrolled epileptic seizures, chronic alcoholism, major trauma, operation etc.) it is advisable to interrupt statins temporarily.

Μυοτοξικότητα από στατίνες: Μια επισκόπηση των παραγόντων κινδύνου

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ΠΕΡΙΛΗΨΗ: Η μυοτοξικότητα είναι η σημαντικότερη ανεπιθύμητη ενέργεια των στατινών, που γενικά θεωρούνται σχετικά ασφαλή και καλά ανεκτά φάρμακα. Βαρύτερη από όλες τις εκδηλώσεις της είναι η ραβδομυόλυση, που είναι δυνητικά θανατηφόρος και χαρακτηρίζεται από νέκρωση μυϊκών ινών. Εκδηλώνεται με μυϊκούς πόνους, αδυναμία, μυοσφαιρινουρία και μεγάλη αύξηση της CPK.

Οι φυσικοχημικές και φαρμακοκινητικές ιδιότητες των στατινών δικαιολογούν την ύπαρξη ορισμένων παραγόντων που ευνοούν την εκδήλωση μυοτοξικότητας. Οι στατίνες μεταβολίζονται κυρίως στο ήπαρ από το σύστημα κυτοχρωμάτων CYP ή P450 σε πιο υδατοδιαλυτά μόρια, ώστε να διευκολυνθεί η απέκκρισή τους. Το σύστημα CYP ή P450 περιλαμβάνει 14 οικογένειες και 20 υποοικογένειες. Τα πιο κοινά ισοένζυμα είναι το CYP3A4 της υποοικογένειας CYP3A και το CYP2C9 της υποοικογένειας CYP2C. Το CYP3A4 εκτός από το ήπαρ ανευρίσκεται επίσης στα επιθηλιακά κύτταρα και στο λεπτό έντερο. Οι μεταβολικές ικανότητες της υποοικογένειας CYP2C αλληλοεπικαλύπτονται από τα διάφορα μέλη της, έτσι ώστε είναι σπάνιες οι έντονες ανεπιθύμητες ενέργειες όταν μια στατίνη μεταβολίζεται από αυτή την υποομάδα ισοενζύμων. Τροφές ή φάρμακα που αναστέλλουν το ένζυμο CYP3A4 ή αποτελούν υπόστρωμα του αυξάνουν την βιοδιαθεσιμότητα των στατινών που μεταβολίζονται από το ίδιο ισοένζυμο και αυξάνουν έτσι την τοξικότητά τους. Η υδροφίλη στατίνη πραβασατίνη έχει το πλεονέκτημα να μεταβολίζεται ελάχιστα από το σύστημα κυτοχρωμάτων CYP και να απεκκρίνεται αυτούσια από τα ούρα και τις κενώσεις.

Παράγοντες κινδύνου που αυξάνουν την πιθανότητα μυοτοξικότητας είναι η μεγάλη ηλικία και το γυναικείο φύλο (για άγνωστους λόγους), γενετικοί λόγοι (μικρότερη έκφραση των δραστικών ισοενζύμων στο ήπαρ και το λεπτό έντερο), η κληρονομική μυοπάθεια, η λιποφιλία που ευνοεί την σύνδεση των στατινών με τις λιπόφιλες μεμβράνες των μυϊκών κυττάρων, οι μεγάλες δόσεις των στατινών, φάρμακα και τροφές που μεταβολίζονται κυρίως με το σύστημα CYP3A4, η νεφρική και η ηπατική ανεπάρκεια, καθώς και οι καταστάσεις που τις επιβαρύνουν.

Λέξεις Κλειδιά: Μυοτοξικότητα, Στατίνες, Κυτοχρώματα CYP ή P450.

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