THE BIOCHEMICAL EFFECTS OF ATORVASTATIN TOXICITY ON THE LIVER AND MUSCLES OF ADULT ALBINO RATS

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ABSTRACT

Background: Statins are considered to be safe, well tolerated and the most efficient drugs for the treatment of hyperlipidemia, one of the main risk factor for atherosclerosis. The safety of statins has been questioned owing to the unacceptable incidence of liver and muscle toxic effects.

Objective: to investigate the effect of Atorvastatin (Lipitor) on the liver and muscles of albino rats, by means of assay of liver enzymes (ALT and AST) and muscle creatine phosphokinase (CPK). **Methods:** 20 adult albino rats were divided into group I (control = 5 rats) and group II (test = 15 rats). Group II rats were given Atorvastatin (Lipitor) daily dose equivalent to human dose of 80 mg/day, for 4 weeks. Assay of ALT, AST and CPK serum levels was done every week. The Drug was stopped for 2 weeks, and levels were measured. Then it was re-introduced for another week, with a final assay of enzymes. **Results:** A significant increase in ALT level <3 × ULN was reached at the end of 4 weeks of drug administration. Upon discontinuation for 2 weeks, a significant drop to normal levels occurred, and when the drug was re-introduced, a mild increase was detected. AST levels were significantly increased at the end of 4 weeks, much higher than that of ALT, and when the drug was stopped for 2 weeks, a decrease of AST occurred but remained higher than normal levels, then increased significantly when Atorvastatin was re-used. Level of CPK was markedly increased to 6 × ULN at the end of 4 weeks, and at the end of 2 weeks of stopping the drug, a significant decrease was recorded that didn't reach the normal level. On re-using the drug, a renewed significant increase occurred. **Conclusion:** The mild increase in ALT with Atorvastatin use, and its normalization when the drug was stopped, suggests a chemical and not structural liver insult. While the disproportionate rise in AST points to an additional muscle effect. The marked increase in CPK suggests a statin-related muscle injury, which needed more than 2 weeks to recover. This highlights the usually mild nature of liver involvement, and the higher risk of statin myopathy, with the need to stop the drug immediately.

Keywords: Atorvastatin - Albino rats - Liver enzymes - CPK.

INTRODUCTION

Atorvastatin, a calcium salt with the trade name Lipitor, is a member of the drug class known as statins. It is a synthetic lipid-lowering agent that lowers blood cholesterol. It also stabilizes plaque and prevents strokes through anti-inflammation and other mechanisms **(Walsh et al., 1996)**.

Atorvastatin is a competitive inhibitor of HMG-CoA reductase. Unlike most others, however, it is a completely synthetic compound. HMG-CoA reductase catalyzes the reduction of 3-hydroxy-3-methylglutaryl-

coenzyme A (HMG-CoA) to mevalonate, which is the rate-limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptors (LDL receptors) on hepatocytes. This increases LDL uptake by hepatocytes, decreasing LDL-cholesterol in blood. Like other statins, it also reduces blood levels of triglycerides and slightly increases levels of HDL-cholesterol **(Villa and Pratley, 2010)**.

The primary uses of atorvastatin are for the treatment of dyslipidemia and the prevention of cardiovascular disease. Decreases in cholesterol levels were dose-related and stable throughout the treatment period. It is recommended to be used only after other measures such as diet, exercise, and weight reduction have not improved cholesterol levels **(Nissen et al., 2006)**.

In addition, statins (including Atorvastatin) have also been shown to target a variety of cellular processes, that modify endothelial function, inflammatory responses, plaque stabilization and thrombogenesis **(Rosenson and Lowe, 1998)**.

Atorvastatin, as well as its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site for cholesterol synthesis and LDL clearance. Lipitor, like other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP) were transient and dose related in severity. Hepatic lesions were reversible with discontinued treatment and dose-related in severity and distribution. Hepatic microgranulomas and hepatocellular degeneration were seen, hepatocellular lipofuscin deposits were also increased. Bile stasis occurred as well. Upon dose reduction, interruption or discontinuation, transaminases returned to or near pre-treatment levels without sequel **(Walsh and Rothwell, 1999)**.

Uncomplicated myalgias have been reported with the use of Atorvastatin. Myopathies, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times upper limit of normal (ULN), should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked CPK elevation. In severe cases, rhabdomyolysis may develop, leading to acute reanal failure **(Hermann et al., 2006)**.

And although hepatotoxicity is more common, myotoxicity may pose a greater risk, especially in cardiac patients. Statins inhibit the synthesis of mevalonate (a precursor of coenzyme Q10) which is a central compound of the mitochondrial respiratory chain, thus affecting cellular respiratory function, resulting in decreased ATP production, that may increase myocardial ischemia, as was shown in animal studies **(Man et al., 2000)**. While in human trials, it was associated with cardiomyopathy with a fall in left ventricular function and diastolic dysfunction **(Silver et al., 2003)**.

But despite the low incidence of statins side effects, their increasing use leads to more physicians encountering these clinical manifestations **(Baker and Tarnopolsky, 2001)**.

This study aims to investigate the effect of Atorvastatin (Lipitor) on the

liver and muscles of albino rats, by means of assay of liver enzymes (ALT and AST) and muscle creatine phosphokinase (CPK).

METHODOLOGY

(A) The Drug:

Atorvastatin (Lipitor) tablets (80 mg) [Pfizer Inc., USA] were used. Tablets were crushed into powder, suspended in water. An amount of 20 mg Atorvastatin was dissolved in 1 mL water. Each rat of the test group was given 1.5 mL/day of the drug suspension, equivalent to a daily therapeutic dose in adult humans of 80 mg/day **(British National Formulary, 2013)**. The dose was calculated according to the interspecies dosage conversion scheme, after **Paget and Barnes (1964)**.

(B) Animals:

Twenty adult albino rats (120 – 170 g) were used in the study. They were kept under good hygenic conditions, fed ad libitum, and allowed free water supply.

(C) Experiemental design:

The rats were divided into 2 groups, as follows:

1- Group I (Control group): contains 5 rats, which didn't receive the drug.

2- Group II (Test group): contains 15 rats, which recieved Atorvastatin (Lipitor) drug suspension for 4 weeks, then the drug was stopped for 2 weeks, and later it was re-introduced for another week.

Body weight was measured weekly for rats of both groups.

(D) Methods:

Blood samples were collected from both groups, obtained from the retro-bulbar venous plexus of the eye, using capillary tubes. Samples were centrifuged immediately at 10000g for 10 minutes. Separated serum was transferred to Eppendorf tubes, which were deeply frozen till the assay time.

Samples were taken at the end of each week, for 4 weeks, then 2 weeks after stopping the drug, and finally 1 week after re-introduction of the drug.

Serum samples were tested for levels of Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and Creatine phosphokinase (CPK).

Assay was done using Beckman Coulter automated chemistry analyzer (spectrophotometer) **(Beckman Coulter, 2014)** at Cairo university hospitals – Chemical pathology department.

STATISTICAL ANALYSIS

Analysis of the data was carried out on a personal computer using Microsoft Excel 2002 software for Windows.

Quantitative variables were described in terms of Mean and SD.

The unpaired t-test was used to compare quantitative variables in parametric data (SD < 50% Mean).

A P-value of more than 0.05 was considered insignificant, whereas that below 0.05 was considered significant. A P-value less than 0.01 was considered highly significant **(Miller and Knapp, 1992)**.

RESULTS

A total of 20 adult albino rats were used in the study, they were divided into two groups: the control group (5 rats) and the test group (15 rats).

Body weight was measured weekly. The mean weight of the control group showed a statistically significant increase ($p < 0.05$) from 135.6±8.7 g at the end of 1st week, to 260.8±5 g at the

end of 7th week. Also, the mean weight of the test group showed a statistically significant increase ($p < 0.05$) from 139.4±9.7 g at the end of 1st week, to 264.8±5.5 g at the end of 7th week.

Table (1): ALT assay values (Mean and Standard Deviation) of Control and Test groups (Normal range 0 – 50 U/L)

	Week 1	Week 2	Week 3	Week 4	Week 6	**Week 7**
Control	**37.6±1.68**	**44±5.2**	**40.8±4.08**	**41.6±2.96**	**39.4±0.88**	40±1.2
Test	53.7±4.95	63.7±5.04	76.4±6.24	84.7±5.65	37.6±3.68	55.4±4.6

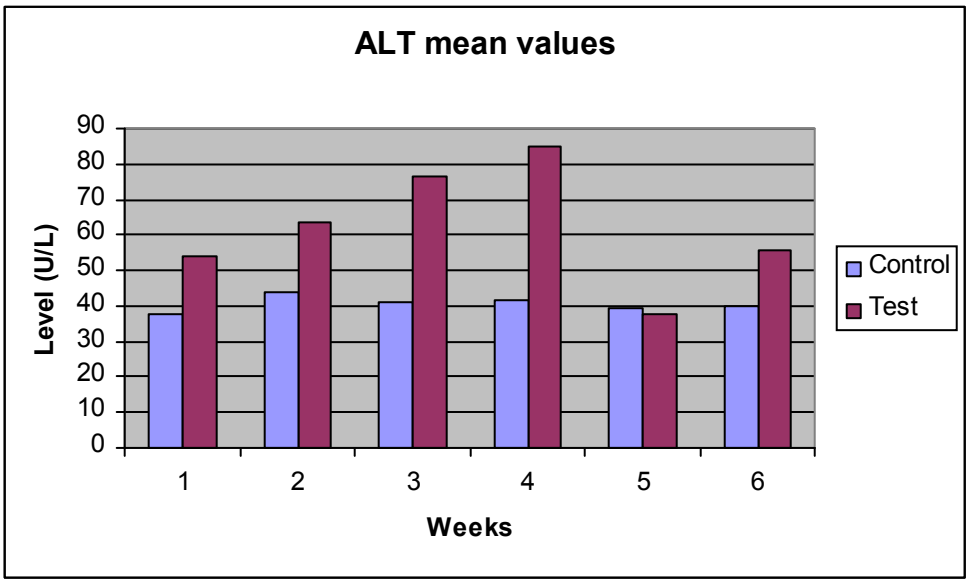

Chart (1): ALT values (Mean and Standard Deviation) of Control and Test groups.

Table (1) and Chart (1) show ALT values (mean and SD) of control and test groups. There was a statistically significant increase ($p < 0.05$) in the test group, at the end of 4th week (84.7±5.65 U/L) compared to the control group (41.6±2.96 U/L). Also, there was a statistically significant increase compared to the 1st week (53.7±4.95 U/L) of the same group. At the end of 6th week (2 weeks after stopping Atorvastatin), there was a statistically significant decrease in the test group (37.6±3.68 U/L) compared to result of 1st week (53.7±4.95 U/L). One week after re-introduction of Atorvastatin, ALT values showed a statistically significant increase in the test group (55.4±4.6 U/L) compared to the control group (40±1.2 U/L), but no significant difference from values of 1st week of the same group.

Table (2): AST assay values (Mean and Standard Deviation) of Control and Test groups (Normal range 0 – 50 U/L).

	Week 1	Week 2	Week 3	Week 4	Week 6	**Week 7**
Control	**41.6±3.52**	**44.2±2.24**	**44.2±3.84**	**47.8±2.96**	**47.2±4.16**	47.8±5.04
Test	145.5±11.5	179.8±10.2	202.5±9.7	224.8±11.7	111.8±9.6	136±7.6

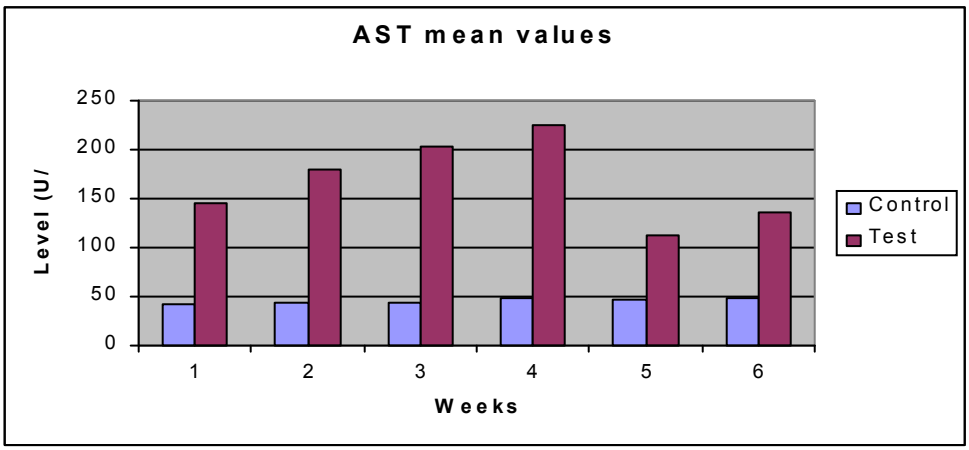

Chart (2): AST values (Mean and Standard Deviation) of Control and Test groups.

Table (2) and Chart (2) show AST values (mean and SD) of control and test groups. There was a statistically significant increase ($p < 0.05$) in the test group at the end of 4th week (224.8±11.7 U/L) compared to the control group (47.8±2.96 U/L). Also, there was a statistically significant increase compared to 1st week (145.5±11.5 U/L) of the same group. At the end of 6th week (2 weeks after stopping Atorvastatin), there was a statistically significant decrease in the test group (111.8±9.6 U/L) compared to the result of 1st week (145.5±11.5 U/L). One week after re-introduction of Atorvastatin, AST values showed a statistically significant increase in the test group (136±7.6 U/L) compared to the control group (47.8±5 U/L), but no significant difference from values of 1st week of the same group.

Table (3): CPK assay levels (Mean and Standard Deviation) of Control and Test groups (Normal range 0 – 145 U/L).

	Weeks 1	Week 2	Week 3	Week 4	Week 6	**Week 7**
Control	**154.4±6**	**157.8±3.4**	**161.8±4.96**	**159.6±5.28**	**158.2±1.76**	162.6±9.1
Test	386.5±45.8	483.8±60.6	707.2±73.4	837±77.2	162.6±14.6	268.4±17.4

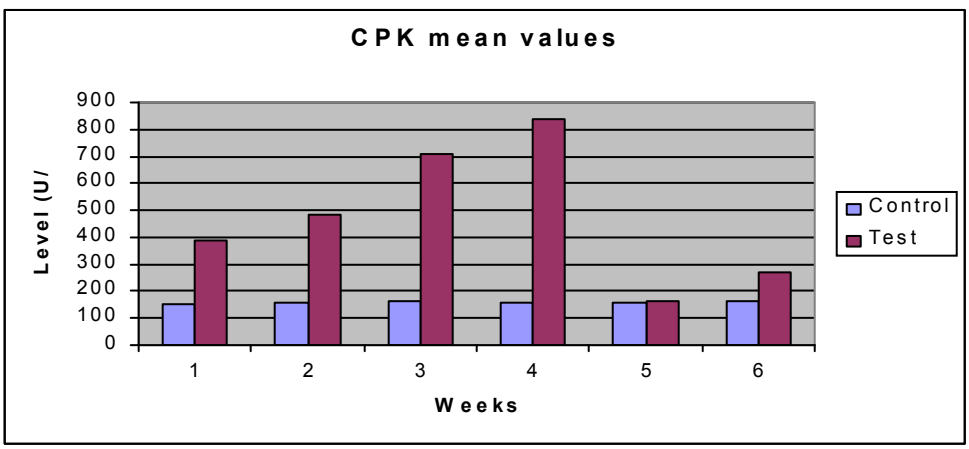

Chart (3): shows CPK assay levels (Mean and Standard Deviation) of Control and Test groups.

Table (3) and Chart (3) show CPK values (mean and SD) of control and test groups. There was a statistically significant increase ($p < 0.05$) in the test group at the end of 4th week (837±77.2 U/L) compared to the control group (159.6±5.28 U/L). Also, there was a statistically significant increase compared to 1st week (386.5±45.8 U/L) of the same group. At the end of 6th week (2 weeks after stopping Atorvastatin), there was a statistically significant decrease in the test group (162.6±14.6 U/L) compared to 1st week. One week after re-introduction of Atorvastatin, CPK values showed a statistically significant increase in the test group (268.4±17.4 U/L) compared to the control group (162.6±9.1 U/L), but there was a statistically significant drop in comparison to values of 1st week of the same group.

DISCUSSION

Statins are inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the rate-limiting step of the cholesterol biosynthetic pathway. As a class, statins are among the most frequently prescribed drugs worldwide. Statins are currently approved and used for reduction of elevated cholesterol levels and cardiovascular risk reduction **(Tobert, 2003)**.

Clinical trials have shown that statins use has been associated with elevations in serum alanine aminotransferase (ALT) levels. Such elevations are not clinically significant in the great majority of cases; and ALT levels greater than 3 times the upper limit of normal (ULN) are seen in only a small minority of patients. With continued use, the mild elevations of serum aminotransferases generally resolve **(Thapar et al., 2013)**.

It was found that in 1% of patients receiving low to intermediate statins dose (10 - 40 mg daily) and in 2% - 3% of patients on high dose therapy (80 mg/daily) ALT elevation occurs **(Cohen et al., 2006)**.

In the present study, ALT values increased significantly upon Atorvastatin administration, and levels reaching <3 × ULN (84.7±5.65 U/L) were recorded at the end of 4 weeks of administration to albino rats. This is similar to the results found in a study provided by **Chang and Schiano (2007)** who reported that generally mild aminotransferases elevation associated with statins occurs within the first 12 weeks and is asymptomatic and improves spontaneously. The large dose used in the present study may account for the early onset of increased ALT levels by the end of 4 weeks instead of 12 weeks. **Illingworth et al. (2001)** found that the rate of liver enzyme elevation with Atorvastatin 80 mg was four times greater compared with Atorvastatin 10 mg.

After stopping Atorvastatin for 2 weeks, ALT values showed a significant decrease to well below the ULN. This confirms that the effect of Atorvastatin on the liver is transient and reversible on discontinuation of the drug, with no residual structural insult. This was proved by previous studies, including that of **Bernini et al. (2001)**.

And upon re-introduction of Atorvastatin, a mild but significant increase in ALT values occurred, nearly the same as in 1st week, suggesting a renewed hepatic effect.

AST values increased markedly after Atorvastatin administration to albino rats, and they nearly reached 5 ×

ULN (224.8±11.7 U/L) by the end of 4th week. This significant elevation doesn't match that of ALT in the same time interval, a condition that can only be explained by the effects of Atorvastatin on muscles, which are also sources of AST, and the higher sensitivity of ALT to hepatic inflammation **(Fraser, 2002)**. When Atorvastatin was discontinued for 2 weeks, AST levels drops significantly (111.8±9.6 U/L) but were still higher than ULN. This also suggests the muscle source of AST elevation. And upon re-introduction of Atorvastatin, a significant but mild increase occurred in AST values, suggesting liver and more probably muscle involvement.

In evaluating unexplained elevations in liver enzymes with statin use, it is also important to exclude myalgia and myositis, which may lead to increases in serum aminotransferase levels, predominantly aspartate aminotransferase (AST) levels, but with far greater increases in serum creatine phosphokinase (CPK) levels **(Thapar et al., 2013)**.

Patterns of liver abnormalities seen with statins include: (1) asymptomatic elevations of ALT: usually transient and mild (ALT <3 × ULN); (2) hepatitis: with ALT >3 × ULN and clinical symptoms of liver disease; (3) cholestatic or mixed hepatitis: with development of jaundice; and (4) autoantibody-associated liver injury **(Russo et al., 2009)**.

The mechanisms behind these adverse effects are unclear, but a few possibilities have been suggested. It has been noted that statins can induce a transient acute phase response on initiation, especially at high doses and this may represent a transient chemical hepatitis due to disturbance of the cholesterol-bile acid pathways **(Wierzbicki et al., 2003)**.

Moreover, it was speculated that the increased transaminases serum activity reflects alterations to the hepatocellular membrane (e.g., enhanced permeability) that permit leakage of these intracellular proteins **(Tolman, 2002)**.

Little consensus exists on how to define the adverse muscle effects of statins, which may contribute to the underdiagnosis of this complication. These effects range from myalgias and myositis to myopathies and rhabdomyollysis. The magnitude of creatine kinase (CK) elevation required to define rhabdomyolysis has increased from 500 U/L in 1982, to 1,000 U/L in 1988, to 50 times the upper limit of normal in one definition **(McKenney et al., 2006)**.

The incidence of statin-induced myopathy is significantly lower in randomized controlled trials of statin efficacy than in observational studies of real-world patients. In randomized clinical trials, myalgia was reported in 1% to 5% of patients in the statin groups and placebo groups alike, whereas clinical practice would suggest it is more common **(Armitage, 2007)**.

The risk of statin-induced myopathy increases with concurrent use of other drugs, e.g. fibrates and and drugs that increase the serum level of statins, e.g. cyclosporine. Increasing the therapeutic dose of the statin also increases the incidence of myopathy **(Evans and Rees, 2002)**.

In this study, a significant elevation in CPK values was registered, reaching nearly 6 × ULN (837±77.2 U/L) at the end of 4th week of Atorvastatin administration. And although this doesn't indicate rhabdomyolysis according to current medical literature

(Gottto, 2003), it still indicates a statin-induced myopathy / myositis. When Atorvastatin was discontinued for 2 weeks, CPK values showed marked drop (162.6±14.6 U/L) but the level was still significantly higher than ULN, suggesting incomplete recovery of muscles and residual structural effects. A longer period of Atorvastatin stopping is needed for healing and reversal of muscle injury, sometimes up to 12 weeks **(Fernandez et al., 2011)**. And when Atorvastatin was re-introduced, a significant increase in CPK (268.4±17.4 U/L) was recorded but it was well below that of the 1st week, suggesting a continued muscle insult.

When myopathy occurs, the stain should be stopped for a sufficient time to allow recovery of muscles, and then another stain is used starting with a smaller dose and monitoring for muscle toxicity. Some statins are more myotoxic than others. It is reported that the incidence of myopathy with Atorvastain use is 14.9% compared to 4.1% in Fluvastain and 18.2% in Simvastatin **(Thompson et al., 2003)**.

The potential mechanisms of statin-induced myotoxicity include intracellular depletion of essential metabolites and destabilisation of cell membranes, resulting in increased cytotoxicity **(Evans and Rees, 2002)**. In addition, reduction in mevalonate metabolites by HMG-CoA reductase inhibitors would affect the activation of certain regulatory proteins responsible for the maintenance and mediation of apoptosis **(Langford and Kendall, 2001)**.

Therefore, it was shown that Atorvastatin administration to albino rats affected the liver, with elevation of transaminases (ALT being more specific to liver insult), and a complete normalization upon stopping the drug, suggesting no structural injury, a condition usually identified as "transaminitis", which is asymptomatic, dose-related and reversible **(Calderon et al., 2010)**.

Elevations in AST levels higher than those of ALT and not dropping to normal levels after discontinuing the drug, point to muscle involvement.

The marked increase in CPK level is an important diagnostic parameter suggesting muscle involvement. And although CPK values didn't exceed 10 × ULN which is required to diagnose rhabdomyolysis, still they indicate the possibility of myositis / myopathy. Failure to reach normal levels after stopping Atorvastatin suggest non-healing of muscle structural insult, which my need prolonged time after withdrawing the drug, and is susceptible to recur upon re-introducing the drug.

CONCLUSION

The beneficial role of statins in primary and secondary prevention of coronary heart disease has resulted in their frequent use in clinical practice. However, safety concerns related to liver and muscle toxicity have resulted in their under-prescription. Therefore, it's recommended that clinicians should screen patients for liver and muscle toxicity regularly during statin administration, and stopping the drug upon detecting marked elevations of ALT or CPK, in addition to clinical manifestations of serious liver or liver involvement.

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التأثيرات الكيميائيه الحيويه للتسمم بعقار أتورفاستاتين على الكبد والعضلات في الفئران البيضاء البالغه

علاء شهاب و ايمان جاب الله
قسم الطب الشرعي و السموم الاكلينيكيه – كلية الطب – جامعة القاهرة

الملخص العربى

تعتبر عقارات الستاتين أكثر أدويه علاج ارتفاع الدهون (وهو أحد عوامل الخطورة الأساسيه لتصلب الشرايين) أمانا وتحملا وفاعليه. ومع ذلك، فهناك تشكيك في سلامة هذه الأدويه نظرا للمعدلات غير المقبوله لحدوث تأثيرات سامة على الكبد والعضلات.

وتهدف هذه الدراسة لفحص تأثيرعقار أتورفاستاتين (ليبيتور) على الكبد والعضلات للفئران البيضاء، بواسطة قياس انزيمات الكبد (ألانين أمينوترانسفيريز، أسبارتيت أمينوترانسفيريز) والعضلات (كرياتينين فوسفوكينيز).

وقد تم استخدام 20 فأر أبيض بالغ، مع تقسيمها الى مجموعة 1 (ضابطة = 5 فئران) ومجموعة 2 (اختبار = 15 فأر)، وتم اعطاء أتورفاستاتين (ليبيتور) للمجموعة الثانيه بجرعة يوميه مكافئة لجرعة الأنسان اليومية المساوية 80 مجم/يوم، لمدة 4 أسابيع. وقد جرى قياس مستويات المصل ألانين أمينوترانسفيريز، أسبارتيت أمينوترانسفيريز و كرياتينين فوسفوكينيز، كل أسبوع. ثم تم أيقاف الدواء لمدة أسبوعين مع قياس المستويات أيضا. وأخيرا أعطي الدواء مرة أخرى لمدة أسبوع مع عمل قياس نهائي للأنزيمات.

وقد تبين حدوث زيادة واضحة في مستوى ألانين أمينوترانسفيريز (أقل من 3 أضعاف أعلى مستوى طبيعي) بنهاية الأسابيع الأربعة من أعطاء الدواء. وعند أيقافه لمدة أسبوعين، حدث أنخفاض واضح وصل للمستويات الطبيعية، ومع أعطاء الدواء مرة أخرى، حدثت زيادة بسيطه في المستوى.

وقد أرتفعت مستويات أسبارتيت أمينوترانسفيريز بصورة واضحة بنهاية الأسابيع الأربعة على نحو أكثر من تلك الخاصه ألانين أمينوترانسفيريز، وعند أيقاف الدواء لمدة أسبوعين، أنخفض المستوى وان بقي أعلى من المستويات الطبيعية، ثم أرتفع بصورة واضحة عند أعادة أستعمال الدواء.

وسجل مستوى كرياتينين فوسفوكينيز أرتفاعا كبيرا (أقل من 6 أضعاف أعلى مستوى طبيعي) في نهاية الأسابيع الأربعة. وبعد أيقاف الدواء لمدة أسبوعين، حدث أنخفاض واضح ولكنه لم يصل ألى المستوى الطبيعي. ومع أعادة أعطاء الدواء، عاد مستوى كرياتينين فوسفوكينيز للأرتفاع بشكل واضح.

وتشير هذه الدراسة ألى أن الزيادة المعتدله في مستوى ألانين أمينوترانسفيريز مع أستعمال دواء أتورفاستاتين، ثم أنخفاضه ألى المستوى الطبيعي مع أيقاف الدواء، ناتجة عن تأثير كبدي كيميائى أكثر منه تركيبي. في حين أن الزيادة غير المتناسبة في مستوى أسبارتيت أمينوترانسفيريز تشير ألى تأثير أضافي على العضلات. وتدل الزيادة الكبيرة في مستوى كرياتينين فوسفوكينيز على أصابة العضلات المرتبطة بعقاقير الستاتين، والتي تحتاج لأكثر من أسبوعين للتعافي. وهذا يبين التأثير البسيط عادة على الكبد، والخطر الأكبر لحدوث أعتلال عضلي ناتج عن عقارات الستاتين، والذي يتطلب أيقاف الدواء فورا.