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RESEARCH ARTICLE

SITAGLIPTIN AMELIORATES ATORVASTATIN INDUCED HEPATOTOXICITY IN RATS

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Abstract

Atorvastatin (ATOR) is the most widely used statin for the treatment of hypercholesterolemia, which is the most common cause of severe liver injury. Sitagliptin is a selective dipeptidyl peptidase-4 inhibitor (DPP4-I) used clinically as oral anti-diabetic agent. This study aimed to identify the effect of sitagliptin (SITA) pretreatment against Atorvastatin (ATOR) induced hepatotoxicity in albino rats. Twenty-five rats were divided into five groups (5 rats in each); normal control, ATOR, SITA and two sitagliptin groups, which pretreated with sitagliptin 10 and 20 mg/kg/day in combination with ATOR 20mg /kg / day for eight consecutive days prior to ATOR. The results revealed that ATOR induced noticeable hepatic injury in the form of moderate Hepatoportal + sinusoidal congestion, all Zonal changes, moderate Cloudy swelling + hydropic degeneration, moderate Fatty change and mild Apoptosis. Biochemical analysis exposed a significant rise in the serum transaminases, alkaline phosphatase and lactate dehydrogenase in ATOR group. Increased Proinflammatory TNF-alpha, Oxidative stress MDA and depressed antioxidant system of GSH were evident in ATOR group. On the other hand, sitagliptin pretreatment significantly ameliorated all of the above mentioned biochemical, histopathological changes induced by ATOR. In conclusion, sitagliptin ameliorated the hepatotoxicity induced by atorvastatin. This effect was probably based through suppression of inflammatory, oxidative stress and apoptotic processes. Sitagliptin might exert beneficial effect on diabetic hepatic disorders which mandate further clinical research.

Keywords: Sitagliptin, Atorvastatin, Hepatoprotective, Statins, DPP4-I, 3MHG-reductase inhibitor.

1. Introduction

The liver is the largest organ in the body, contributing about 2% of the total body weight, or about 1.5 kilograms (3.3 pounds) in the average adult human. The basic functional unit of the liver is the *liver lobule*, the liver which is the important organ for metabolism different substances including drugs [1]

Hepatotoxicity is an injury to the liver that is related to retired liver function caused by the administration of drugs or other noninfectious agents such as prescription drugs, over the counter OTC, daily supplements, special food and environmental chemicals, and xenobiotics. [2]. Drugs are the largest causes of hepatotoxicity, usually resulting adverse drugs reactions [3, 4].

One of the frequently prescribed drugs that cause hepatotoxicity is statins. [5]. Statins are the first-line therapy for hyperlipidemia. These drugs block the corner stone in cholesterol synthesis by inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, and cause marked decreasing in low density lipoprotein LDL-C [6].

Among various medically used statins, atorvastatin (ATOR) is the most widely used statin for the treatment of hypercholesterolemia [7, 8]. Moreover, ATOR is the most common cause of severe liver injury where lethality can be seen at high dose [9]. Studies have shown that ATOR significantly increased transaminase levels three times the upper limit of normal value [10]. In addition, it has been reported that liver damage occurred in 1.9%-5.5% of patients who have taken statins and a substantial proportion (34%) of these cases caused liver injury by ATOR [7].

Achieving a very low level of LDL- cholesterol at a higher dose of ATOR in patients with coronary heart disease, ATOR has proved more effective than

lovastatin, pravastatin, Fluvastatin and simvastatin in reaching target LDL-cholesterol levels at high doses [11]

Previous reports have established the essential role of oxidative stress in ATOR hepatotoxicity. Extreme generation of reactive oxygen and nitrogen species, laterally through decreased antioxidant protection device help the development and progression of hepatotoxicity [12]. Recent studies have shown the probable role of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase in mediating ATOR-induced hepatotoxicity [13]. It has been shown that ATOR was the most associated with hepatotoxicity in diabetes mellitus (DM), where Shu et al. confirmed the ATOR induced hepatotoxicity in rats with DM [9].

Sitagliptin (SITA) is oral hypoglycemic, which is recently used for treatment type 2 DM. It inhibits the dipeptidyl – peptidase 4 (DPP-4) enzyme and subsequently, elongation the post-prandial alacrity of glucagon – like – peptide – 1 (GLP-1). [14]. DPP-4 distributes mainly in all body systems and has pleotropic biological actions, it is thought that DPP-4 is responsible for the modification of a number of regulatory factors that contain peptides and chemokine affecting the signaling functions. Therefore, it has been suggested that DPP-4 involves in pinpointing immune response and management of inflammatory disorders [15].

Especially SITA in experimental studies induced steatohepatitis by modulation lipid metabolism, oxidative stress and anti-inflammatory [16, 17]. Additionally, hepatoprotective effect of SITA has been shown against induced hepatotoxicity in animal models studies [18, 19]. Notably, sitagliptin has exposed hepatoprotective action in experimentally induced steatohepatitis via modulation of lipid metabolism, oxidative stress and inflammatory mediators [16, 17]. Though, the precise mechanism of its hepatoprotective activity is multifaceted and not totally explained.

To the best of our knowledge, the outcome of sitagliptin against ATOR-induced hepatotoxicity has not been verified. Therefore, the current study aimed to clarify the probable effect of sitagliptin on ATOR-induced hepatotoxicity. Results of this study might add helpful information in the field of liver toxicity.

2. Materials & Methods

2.1. Study Duration and sitting

The study was carried out in animal house at Faculty of Pharmacy, University of Aden during the period from July to September 2023.

2.2. Study design

The type of design was an experimental study, where quantitative and qualitative variables was included.

2.3. Sample size

Twenty-five healthy male albino rats weighing (180-250 gm) were used in this study.

Sample size was calculated by:

E = Total number of animals – Total number of groups

E= 25-5, E=20, so E lies within 10 to 20 for optimum sample size [20]. Therefore, 25 animals will be used in this experiment.

2.4. Materials

2.4.1 Chemicals

The chemicals used in the experiment were normal saline 0.9% solution (Amanta Healthcare Limited – India), 10% formalin (Isochem – Laboratories- India), Paraffin (Numaligarh Refinery Limited – India), Ketamine (Rotixmedica – Germany), Hematoxylin and eosin Kit (Benz microscopic optic – Ireland)

2.4.2. Drugs

The drugs for the experiment were Atorvastatin powder 99% pure, Sitagliptin powder 99% pure (were received as a gift from Yemenia- Egyptian company and modern drug company)

2.5. Instruments and Equipment

The instruments used were Electronic balance (Spanish - LABORCOM), Sensitive Electronic balance (Spanish – P SELECTA), Centrifuge (Spanish – P SELECTA) Screen master plus - Biochemical system international SrI(Italy- IVD), Eliza (USA - Star Fax 4700)

2.6. Treatment of Animals

Albino rats were housed in cages under standard laboratory condition (temperature-controlled environment (20 -25°C) with a 12:12-hour cycle for light and dark with relative humidity 55-60%). They were handled according to animal ethics guide. Standard diet and tap water ad libitum were available to them without charge. In addition, they were adapted to this condition for 1 week before starting the procedure. The housing was in the pharmacology animal house at the Faculty of Pharmacy - Aden University

2.7. Methods

2.7.1 Drugs / sample preparation

2.7.1.1 Atorvastatin preparation

99% pure ATOR was obtained as a gift from Gift from Yemenia- Egyptian Company and modern drug company

2g of it was dissolved in 100 ml of distilled water (2%) yielding 20 mg atorvastatin in 1 ml-distilled water, which will be ready for administration [21].

2.7.1.2 Sitagliptin preparation

(SITA 20 mg/kg b.w) and (SITA 10mg /kg b.w) were prepared from 99% pure powder freshly dissolved in normal saline.

2.7.2 Experimentation

The study was carried out with 25 rats. The animals were randomly divided into 5 groups each group containing 5 rats as the following:

Group I (Normal control- NC), Group II (ATOR group), Group III (SITA 10), Group IV (SITA 10 + ATOR 20), Group V (SITA 20 + ATOR 20) [22].

Group I: in which the rats were receive normal saline throughout the experimentation.

Group II: in which ATOR (20mg/kg b.w) was given at the 8th day until the 28th day (end of experimentation).

Group III: SITA in which the rats were treated with SITA (10 mg/kg b.w) from the first day until the end of experimentation.

Group IV: where the rats were treated with SITA (10 mg/kg b.w) at the first 7 days, then ATOR (20mg/kg b.w) was added in 8th day and both continue until the end of the experimentation.

Group V: where the rats were treated with SITA (20 mg/kg b.w) at the first 7 days, then ATOR ((20mg/kg b.w) were added at the 8th day and both continue until the end of the experimentation.

The selection of 28 days for the treatment period is appropriate and based on previous studied approved its efficiency [21, 19].

2.7.3. Experimental methods

2.7.3.1. Spectrophotometer Test

2.7.3.1.1. Serum Enzymatic activity

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) were measured following the steps of the instruction manual supplied by AGAPPE Lab by using a spectrophotometer. Samples of venous blood were drawn via a capillary tube from the orbital-sinus capillary vein. The blood was put into the test tubes, allowed to clot for 20 minutes, and then centrifuged at 4000 g for 20 minutes. The (ALP), (ALT), and (AST) enzyme levels in the serum were analyzed later after collection and storage at 4°C [23]. The unit of measurement for enzyme activity is the international unit per liter (IU/L).

2.7.3.2. Eliza Test

2.7.3.2.1. Determination of proinflammatory cytokine in the serum of the rats

Serum tumor necrosis factor alpha (TNF-α) was measured following the steps of the instruction manual supplied by the BT- LAB ELISA kits.

2.7.3.2.2. Determination of oxidative stress markers in the serum of rats

Serum reduced glutathione (GSH) and malondialchehyche (MDA) were measured following the steps of the instruction manual supplied by the BT- LAB ELISA kits.

2.7.3.3 Histopathological examination

Liver tissues were fixed in a buffer solution containing 10 % formalin and processed for routine paraffin block preparation. Sections of 5 µm were cut and stained with hematoxylin and eosin stain (H&E) for histological examination. [18]. The tissue processing was done at Histology I- Lab laboratories in Aden – Yemen.

2.8. Statistical Analysis

Data were checked then entered the Statistical Package for Social Sciences (SPSS) software version 27 (IBM SPSS Inc. Chicago, Ill, USA)). All results were presented as the mean ± SD. Treatment group means were compared by one-way ANOVA followed by post hoc Tukey's test for pair-wise comparisons. $P \leq .05$ was considered statistically significant for all tests.

2.9. Ethical Consideration

This study was approved by the Animal Ethical Committee at Faculty of Medicine and Health Sciences – University of Aden (REC- 156-2023). Animal handling was done according to The Norwegian National Research Ethics Committees. Ethical Guidelines for the Use of Animals in Research. 1st edition, 2018. Available at: www.etikkom. After scarify, the animal's body were buried.

3. Results

Twenty-five rats were used in this in vivo experimental study to investigate the effect of sitagliptin on atorvastatin induced liver injury in albino rats. After one week of adaptation, the body weight of each rat was measured three times and the mean weight was calculated and presented in table 3.1. The rats were divided spontaneously into five groups, each with five rats. The mean weight of the groups showed in table 3.1.

Table 3.1. Rats weight among groups

Groups n = 5	CN (gm) n = 5	ATOR (gm) n = 5	SITA10 (gm) n = 5	SITA10+ATOR20 (gm) n = 5	SITA20+ATOR20 (gm) n = 5
1	290	200	256	204	246
2	284	210	213	208	235
3	300	221	232	295	230
4	295	216	210	269	265
5	298	230	232	227	250
Mean±SD	293±7	215±11	228.6±18	241±40	245±33
Maximum	300	230	256	285	300
Minimum	284	200	210	204	200

Table 3.2. Effects of Atorvastatin (ATOR) and Sitagliptin (SITA) on biochemical parameters of liver function

Groups	ALT (IU/L) Mean ±SD	AST (IU/L) Mean ±SD	ALP (IU/L) Mean ±SD	LDH (IU/L) Mean ±SD
NC	43.8±10	76.2 ±14	149±40	750±188
ATOR	133.2±25**	160±22**	336±28***	1990±211$^{\#\#\#}$
SITA 10	69.6±26$^{\#\#}$	72.6±26$^{\#\#}$	154±23$^{\#\#\#}$	1355±546
SITA 10mg + ATOR 20 mg	76.7±17$^{\#}$	123±28*	252±29$^{**\#\#\#}$	1606±382**
SITA 20mg + ATOR 20mg	57±33.9$^{\#\#}$	124.2±19*	251±51$^{**\#\#\#}$	1571±300*

NC = normal control group, ATOR = Atorvastatin 20mg group, SITA = Sitagliptin 10mg group, SITA 10 +ATOR 20 = sitagliptin 10mg + Atorvastatin 20mg, SITA 20+ATOR20= sitagliptin 20mg+Atorvastain 20mg.

All data are expressed as Mean ± SEM (n=5/group. *p <0.05, **p <0.01, ***p <0.001 vs NC, #P <0.05, ##P <0.01, ###P <0.001vs DC.

3.1. Rats weight

A total of 25 rats were weighted in this study. their mean 244.6 ± 33.3 gm, the Minimum = 200 gm and Maximum = 300 gm

3.2. Effect of sitagliptin on Atorvastatin induced LFT

ATOR treatment increased the serum activities of ALT, AST, ALP and LDH compared to the NC group.

Pretreatment with SITA caused a significant reduce in hepatic transaminases, ALP and LDH levels compared to ATOR group in a dose dependent manner. See table 3.5

3.3. Effect of Sitagliptin on Atorvastatin-induced inflammatory biomarker

3.3.1 Effect of sitagliptin on atorvastatin-induced TNF alpha in serum

The levels of serum TNFa were significantly increased in ATOR group than those in NC group (ATOR, 77 ng/L vs 45 ng/L NC, P = 0.004. in contrast, significant reduction was observed in the levels TNFa upon SITA treatment at dose (20mg/kg, 10mg /kg) in combination with ATOR 20mg/kg by (33.7 %, 42.8%) (p=0.01, p=0.003) respectively. The results were comparable with ATOR group. While reduction not significant in SITA 10mg /kg alone by (35%) compare to ATOR group. Table 3.6

Table 3.3. Effect of sitagliptin on atorvastatin-induced TNF alpha in serum

Groups	TNFa (ng/L) Mean ±SD	P Value
NC	45±10	
ATOR	77±16	0.004**
SITA 10	50±12	0.20
SITA 10mg + ATOR 20 mg	44±6	0.003$^{\#\#}$
SITA 20mg + ATOR 20mg	51±13	0.01$^{\#}$

NC = normal control group, ATOR = Atorvastatin 20mg group, SITA = Sitagliptin 10mg group, SITA 10 +ATOR 20 = sitagliptin 10mg + Atorvastatin 20mg, SITA 20+ATOR20= sitagliptin 20mg+Atorvastain 20mg.

All data are expressed as Mean ± SEM (n=5/group. **P < 0.01vs NC, $^{\#}$P <0.05, $^{\#\#}$P <0.01 vs DC.

3.4. Effect of Sitagliptin on Atorvastatin-induced oxidative stress biomarkers

The levels of serum MDA was significant increased and serum GSH was significantly decreased in ATOR group than those in NC group.

In contrast, highly significant reduction was observed in the level's serum MDA upon SITA treatment at dose (20mg/kg) in combination with ATOR 20mg/kg by (77 %) (p < 0.001) and significant reduction in levels of MDA upon SITA (10mg/kg) alone by (60%) (p=0.02). the results were comparable with ATOR group. while reduction not significant in SITA treatment at dose (10mg /kg) in combination with ATOR (20mg/kg) by (39.1%) compare to ATOR group. on the other hand show significant elevated of GSH serum in SITA treatment at dose (10mg /kg) alone by (47.7 %) compare to ATOR group.

Table 3.4. Effect of sitagliptin on atorvastatin-induced oxidative stress in serum

Groups	MDA (nmol/ml) Mean ±SD	P Value	GSH (mg/L) Mean ±SD	P Value
NC	0.64±0.2		64.36±8.7	
ATOR	2.3±0.8	< 0.001***	30.63±5.9	0.001**
SITA 10	0.90±0.5	0.02#	58.65±4.8	0.007##
SITA10mg + ATOR 20 mg	1.4±0.5	0.53	51.92±18.4	0.05
SITA20mg + ATOR 20mg	0.58±0.1	< 0.001###	48.14±12.6	0.1

NC = normal control group, ATOR = Atorvastatin 20mg group, SITA = Sitagliptin 10mg group, SITA 10 +ATOR 20 = sitagliptin 10mg + Atorvastatin 20mg, SITA 20+ATOR20= sitagliptin 20mg+Atorvastain 20mg.

All data are expressed as Mean ± SEM (n=5/group. **p <0.001, ***p <0.001 vs NC, #P <0.05, ##P <0.01 ###P <0.001 vs DC.

3.5. Effects of SITA on histopathological changes in ATOR-induced hepatotoxicity

To verify the model's successful development, the pathogenic characteristics of ATOR-induced hepatotoxicity were observed in NC group and compared with the other study groups. Liver tissue sections from normal rats disclosed that Hepatoportal + sinusoidal congestion normal, Zonal change, Cloudy swelling + hydropic degeneration, Fatty change, Apoptosis, Inflammatory cellular infiltrate, Fibrosis, Cholestasis and Cellular necrosis were not seen (Figs. 1 NC).

ATOR-induced noted histopathological changes in liver on DC group, such as moderate Hepatoportal + sinusoidal congestion, all Zonal had changes, moderate Cloudy swelling + hydropic degeneration, moderate Fatty change and mild Apoptosis.

SITA 10 group rats with dose of sitagliptin (10mg/kg) showed mild Hepatoportal + sinusoidal congestion, mild Cloudy swelling + hydropic degeneration, mild Apoptosis and there are not zonal changes and not seen fatty changes, apoptosis, Inflammatory cellular infiltrate, Fibrosis, Cholestasis and Cellular necrosis.

These effects were similar to those seen in the SITA 10+ATOR 20 and SITA 20+ATOR 20 groups, while peripheral Zonal change in the above histopathological changes was reported in ATOR-induced rats treated with two doses of SITA (10, 20mg/kg) and there are not seen Cloudy swelling + hydropic degeneration in ATOR-induced rats treated with dose of SITA (20mg/kg). Furthermore, combined therapy showed profoundly synergistic efficacy in repressing these alterations in liver sections.

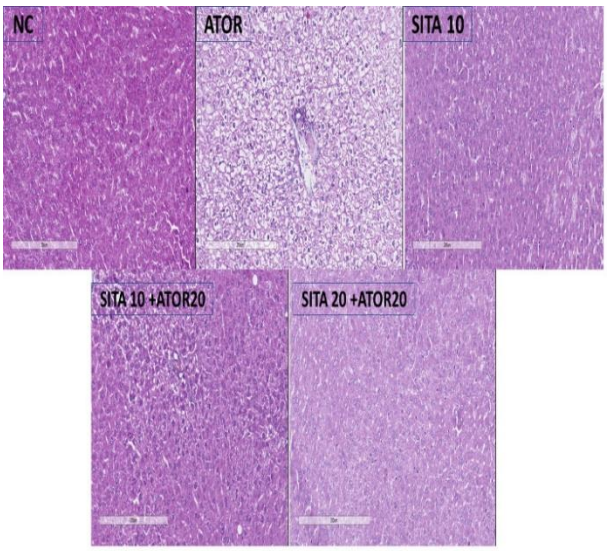

Fig. 1: Sitagliptin (SITA) pretreatment ameliorates Atorvastatin (ATOR)-induced histopathological lesions in liver of rat (H&E stain, 200×)

Effects of Sitagliptin (SITA) (SITA 10 and 20 mg/kg) on ATOR-induced hepatotoxicity in Liver histology of rats. Hematoxylin and eosin (H&E, 10x.), stained liver tissue sections from rats in the normal control group show normal liver structures. In contrast, ATOR group showed moderate Hepatoportal + sinusoidal congestion, all Zonal changes, moderate Cloudy swelling + hydropic degeneration, moderate Fatty change and mild Apoptosis. Considerable restoration of the liver architecture and modulation of Hepatoportal + sinusoidal congestion, Cloudy swelling + hydropic degeneration, Apoptosis and there are not zonal changes and not seen fatty changes, apoptosis, Inflammatory cellular infiltrate, Fibrosis, Cholestasis and Cellular necrosis. SITA 10 (10mg /kg alone), SITA 20+ATOR20 (sitagliptin 20mg/kg + atorvastatin 20mg/kg), SITA 10+ATOR 20(sitagliptin 10mg/kg + atorvastatin 20mg/kg), respectively.

4. Discussion

The present study investigated the effect of sitagliptin on atorvastatin induced liver injury in albino rats by biochemical and histopathological testing. The findings of this study showed that atorvastatin (20mg/kg) induced

liver injury manifested as raised serum levels of liver enzymes. This result is in line with Shoaib *et al*. from Jordan [24]. Pre-treatment with sitagliptin reduces the ATOR elevated serum levels of liver enzymes. This finding agrees with the report of Abo-haded et al. from Saudi Arabia [19, 25]

It has been reported that 20mg dose of ATOR, as used for treatment of hyperlipidemic has been associated with organ toxicity including acute hepatotoxicity, progressive hepatic fibrosis and fatty change [26, 21, 12]. Results of the present study showed that rats treated with ATOR showed marked liver injury as indicated by significant increase in liver transaminases, ALP and LDH, which represent the most reliable markers of liver necrosis as cytosolic enzymes. An increase in their activity in the serum is linked to hepatocyte mortality, because it signifies a cell membrane leak [27, 28].

The enzyme known as alanine aminotransferase (ALT) is responsible for catalyzing the transfer of amino groups to create oxaloacetate, a metabolite found in the liver. One It consists of 496 amino acids, which are produced by a gene found on chromosome 8's long arm. The hepatocyte's cytosol contains a large amount of ALT [29].Therefore, measured ALT activity in the serum is increased in cases of hepatocellular injury or death due to the release of ALT from damaged liver cells. Though it is commonly believed to be unique to the liver, it can also be found in the kidney, heart, and skeletal muscle cells, although in much lesser amounts. The liver catabolizes ALT that is discharged into the blood [30].

A possible hepatic toxicity is indicated by an increase in aminotransferases levels greater than three times the upper normal limit [31]. A rise in ALT and AST has been observed in previous atorvastatin studies [32, 26, 21]. This study showed a similar impact, with elevated ALT and AST (2–3 times the baseline) indicating mild liver damage.

In the present study, the administration of SITA at a dose of 10 mg/kg b.w before ATOR showed a reduction in ALT level by 42.5% (from ATOR group 133.2 IU/L to 76.7.IU/L in SITA 10 mg/kg group), while a dose of 20 mg/kg reduces the level of ALT by 57.3%. this finding of cumulative effect and dose dependent effect is in line with that finding demonstrated by Abo-haded et al [25, 19]. In the same study of Abo-haded et al, they tested SITA (20mg/kg) for possible induction of effect in experimental rats, and found slight change in ALT level from the control. This finding supports our results in which 10mg/kg and 20 mg/kg SITA did not show significant difference with ALT levels of the control group.

At basic pH levels, the ubiquitous glycoprotein attached to membranes named alkaline phosphatase catalyzes the hydrolysis of phosphate monoesters. Depending on the region of tissue expression, alkaline phosphatase is classified into four isozymes: tissue nonspecific alkaline phosphatase, often known as liver/bone/kidney ALP; intestinal ALP; placental ALP; and germ cell ALP[33]. The results of this investigation demonstrated that ALP levels in serum were significantly elevated following ATOR treatment, and addition of SITA before ATOR reduced ALP levels that ewer dose-dependent. This outcome agrees also with the results of Abo-haded et al.

The enzyme lactate dehydrogenase (LDH) catalyzes the simultaneous interconversion of NADH and NAD + with pyruvate and lactate [34]. When oxygen is scarce or nonexistent, it changes pyruvate into lactate; when oxygen is present, it reverses the reaction during the liver's Cori cycle. Red blood cells, muscles, liver, and kidneys all contain large levels of LDH. Increased LDH levels could be a sign of liver injury [34, 35, 36].

Our investigation's finding showed that serum LDH levels were noticeably higher after ATOR-induced. and that after receiving SITA medication, LDH levels were dose-dependently lowered but not significantly. Explanation for this finding may be that LDH is not a specific liver- enzyme like ALT and AST[36] another reason could be a function of SITA dosing implicated in non-significant result, or a necessity for a longer treatment course with SITA to achieve an LDH reduction.

Proinflammatory cytokine TNF-α is generated by several kinds of inflammatory cells and contributes to the innate immune response. It is essential for the first line defense of the host mounts against invaders and is a key mediator of the inflammatory response. It increases oxidative damage by inducing the release of other cytokines and nitric oxide [37]. Previous studies have suggested a role of inflammatory responses in the progression of ATOR-induced toxicity[12, 38] The present study showed increment in serum levels of TNF-α associated with liver damage due to ATOR administration, which was reduced after treatment with SITA. The reduction was does dependent. These findings are consistent with earlier research data displaying the capacity of sitagliptin to block the production of several cytokines including TNF-α [18, 19]. It could be concluded that SITA possesses anti-inflammatory effect.

It is interesting to find that the significance (p=0.003) in reduction of TNF-α by 10 mg/kg SITA result was higher than that by 20mg/kg (p=0.01). This result is in line with[18]. It is worth to mention that the results about SITA effect on TNF-α by Abo-haded et al recorded the same statistical significance by both 10mg/kg and 20mg/kg SITA in TNF-α reduction induced by ATOR.

Clinical investigations and animal research have demonstrated the impact of oxidative stress on the development of hepatotoxicity [39].

The involvement of ROS/RNS in the pathophysiology of ATOR-induced hepatotoxicity has been shown in earlier investigations. When these extremely reactive organisms interact with biological macromolecules, they produce lipid peroxides, inactivate proteins, and cause mutations. They also significantly change the oxidant/antioxidant equilibrium, increasing MDA levels while decreasing GSH content activity. [12, 7].

Increased tissue damage linked to lipid peroxidation is the cause of the elevated MDA levels in ATOR-treated groups. Most studies approve that increased lipid peroxidation plays a significant role in the development of many acute and chronic diseases as well as in the onset of oxidative stress associated different tissue damage and cell death [40]

The study revealed increment (almost three and halftime of the control value) in serum level of MDA when rats treated with 20mg AOTR compared to the control group. The difference between the groups was highly significant. Pretreatment with 10 mg/kg SITA reduced almost two time the elevated level of ATOR induced MDA level, while 20mg/kg dose produced four time reduction of ATOR elevated MDA level. The difference was statistically significant. This finding may describe the protective effect of SITA against ATOR induced-hepatotoxicity. The results are in line with [18], with the exception of non-significant effect of 10mg SITA.

The primary antioxidant system that prevents oxidative stress injury and is crucial for the detoxification of harmful chemicals on the liver is GSH and its related enzymes [18]. Previewed studies demonstrated that, ATOR can decrease the GSH level [13]which is in the same line with study investigation that showed a reduction in GSH. Administration of sitagliptin (10mg and 20 mg) with ATOR increased the level of GSH that may ameliorates the progression of hepatic fibrosis due to inhibition of oxidative stress. But the difference between the groups were insignificant. Nevertheless, this may highlight the beneficial effects of sitagliptin. Moreover, given alone to rats, 10 mg/kg SITA significantly raised serum GSH levels.

Hereby, in our attempt to validate if sitagliptin may possess hepatoprotective action against ATOR-induced hepatotoxicity, the beneficial effects found in this study might be mediated by a reduction in liver enzymes, inhibition of inflammatory markers and reduction of oxidative stress biomarker this corollate with histopathological changes. This finding is in line of [18, 15].

The histopathological examination results, which showed significant liver injury in the ATOR-induced group, corroborated to the biochemical abnormalities, inflammatory biomarker and oxidative stress with agreement to [12]. The pretreatment with sitagliptin considerably reduced these biochemical and histological alterations, indicating that sitagliptin might effectively prevent liver cell injury caused by ATOR. Our histopathological findings showed that ATOR effectively cause moderate Hepatoportal + sinusoidal congestion, all Zonal had changes, moderate Cloudy swelling + hydropic degeneration, moderate Fatty change and mild Apoptosis. Thus, histopathological changes are remodeling and its modulations by SITA in the literature correlated well with the histopathological data of our experiments [25, 19].

Conclusion

The study concluded that atorvastatin induced hepatotoxicity in rats by increasing serum aminotransferases, ALP and LDH that coincide with increasing in levels proinflammatory (TNF- alpha) and oxidative stress biomarker (MDA) and decreased level of serum GSH with histopathological changes in liver tissues. Sitagliptin in dose dependent manner alleviated atorvastatin induced liver injury as evident in histopathological changes. The anti-inflammatory and antioxidant properties of sitagliptin might be of benefit for diabetics which requiring further studies.

Recommendation

Farther research is required to investigate and explore the molecular mechanisms stand behind protective effect of sitagliptin in the liver.

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مقالة بحثية

دواء سيتاجليبتين يخفف من السمية الكبدية التي يسببها أتورفاستاتين في الفئران

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المُلخّص

أتورفاستاتين يعتبر من مجموعة الاستاتين الأكثر استخداما لعلاج فرط كوليسترول الدم، وهو السبب الأكثر شيوعا لإصابة الكبد بالسمية. بينما دواء سيتاجليبتين هو مثبط انتقائي لثنائي الببتيداز-4 يستخدم سريريا كعامل مضاد للسكري عن طريق الفم. تهدف هذه الدراسة إلى تحديد تأثير المعالجة المسبقة لسيتاجليبتين ضد السمية الكبدية التي يسببها أتورفاستاتين في الفئران البيضاء. تمت هذه الدراسة على خمسة وعشرين فأرا تم تقسيمهم إلى خمس مجموعات (5 فئران في كل منها)؛ المجموعة الطبيعية، مجموعة الاتور، مجموعة السيتا 10، ومجموعتان من سيتاجليبتين، والتي عولجت مسبقا بسيتاجلبتين 10 و20 ملجم /كلجم/ يوم بالاشتراك مع أتورفاستاتين 20ملجم / كلجم / يوم لمدة ثمانية أيام متتالية قبل أتورفاستاتين واستمرارهم ثمانية وعشرون يوما. كشفت النتائج أن أتورفاستاتين تسبب في إصابة كبدية ملحوظة على شكل احتقان كبدي معتدل +، وتغير في جميع التغيرات مناطق الكبد، وتورم في خلايا الكبد معتدل + تنكس مائي، وتغير دهني معتدل، وموت الخلايا المبرمج، كشف التحليل الكيميائي الحيوي عن ارتفاع كبير في انزيمات الكبد (ترانزامينيز) وانزيم الفوسفاتيز القلوي وانزيم هيدروجين اللاكتات، كانت هناك زيادة في مؤشرات الالتهاب (**TNF-alpha**)، والإجهاد التأكسدي (**MDA**) ونقص في نظام مضادات الأكسدة (**GSH**) واضحة في مجموعة الفئران التي اعطي لها أتورفاستاتين. من ناحية أخرى، خففت المعالجة المسبقة لسيتاجليبتين بشكل كبير جميع التغيرات البيوكيميائية والنسيجية المرضية المذكورة أعلاه التي يسببها أتورفاستاتين. خفف سيتاجليبتين من السمية الكبدية التي يسببها أتورفاستاتين. ربما استند هذا التأثير من خلال قمع الإجهاد الالتهابي والتأكسدي وعمليات موت الخلايا المبرمج. قد يكون لسيتاجليبتين تأثير مفيد على الاضطرابات الكبدية السكرية التي تتطلب المزيد من الأبحاث السريرية.

الكلمات المفتاحية: سيتاجليبتين، أتورفاستاتين، حماية الكبد، ستاتين، مثبط انتقائي لثنائي الببتيداز-4، مثبطات اختزال ثلاثي هيدروكسي – ثلاثي جلا تريل.

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