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Hepatoprotective effects of simvastatin on paracetamol -induced hepatic damage in rats

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ABSTRACT: *This study was designed to investigate the possibility of statins hepatoprotection in paracetamol toxicicity. Paracetamol hepatotoxicity was associated with significant decrease in the serum total albumin(g/dl) p< 0.05) and total protein(g/dl) (p< 0.05) . However, it significantly increased (p< 0.0001), ALT IU/L, AST IU/L, and ALP IU/L as shown in group 3 (positive control) in comparison with the negative control (group 1) (table 1). Using of simvastatin 10mg/kg in healthy animals (group 2) caused slight insignificant changes in serum total albumin(g/dl), total protein(g/dl), ALT IU/L, AST IU/L, and ALP IU/L. However, simultaneous administration of simvastatin 10mg/kg with paracetamol, significantely attenuate the adverse changes in the serum total albumin(g/dl), total protein (g/dl), ALT IU/L, AST IU/L, and ALP IU/L. However, it didn't bring them to the normal limits.*

KEYWORDS: *Paracetamol, hepatotoxicicity, hepatoprotection, simvastatin*

I. INTRODUCTION:

Paracetamol overdose is a major cause of acute liver failure. The glutathione (GSH) precursor *N*-acetylcysteine (NAC) is used to treat patients with paracetamol overdose for up to 48 hours. Although it is well established that early treatment with NAC can improve the scavenging of the reactive metabolite *N*-acetyl-*p*-benzoquinone imine, protective mechanisms at later times remain unclear [1].

However, many other drugs were used as hepatoprotective in paracetamol poisoning such as angiotensin converting enzyme inhibitors or angiotensin receptor II antagonists, Hydrogen-rich water, resveratrol, melatonin, quercetin and other flavonoids and many other drugs [2-7]. On the other hand modern research also showed that a wide range of plants can neutralize or detoxify toxins and protect hepatic system from the toxic effects of drugs and chemicals. These plants included: *Agrimonia eupatoria*, *Alhagi maurorum*, *Allium sativum*, *Alpinia galangal*, *Anchusa strigosa*, *Arctium lappa*, *Artemisia campestris*, *Asparagus officinalis*, *Astragalus hamosus*, *Bauhinia variegata*, *Benincasa hispida*, *Brassica nigra*, *Brassica rapa*, *Bryonia dioica*, *Bryophyllum calycinum*, *Caesalpinia crista*, *Calendula officinalis*, *Calotropis procera*, *Canna indica*, *Capparis spinosa*, *Capsella bursa-pastoris*, *Capsicum frutescens*, *Capsicum frutescens*, *Carthmus tinctorius*, *Carum carvi*, *Cassia occidentalis*, *Casuarina equisetifolia*, *Celosia cristata* and *Chenopodium album* [8-51]. The 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (*ie*, statins) are widely used for the treatment of patients with hyperlipidemia and ischemic heart diseases. But, there is growing interest in the use of statins, HMG-CoA reductase inhibitors, as neuroprotective and for treating specific neurodegenerative diseases (e.g., cerebrovascular disease, Parkinson's disease, Alzheimer's disease, multiple sclerosis) and possibly traumatic brain injury [52]. Furthermore, they were also used to protect lungs from emphysema and chronic obstractive pulmonary diseases occure as a result of smoking [53]. Statins also conferred 70-90% hepatic protection against ischemia-reperfusion injury in obese animals with steatosis or non-alcoholic steatohepatitis [54]. Therefore this study was designed to investigate the possibility of statins hepatoprotection in paracetamol toxicicity.

Materials and Methods:

Paracetamol (SDI Co, Iraq) and Simvastatin (Actavis, Barnstaple, EX32, UK) were dissolved in normal saline before use.

Animals Male Sprague-Dawley rats, weighing 250 ± 10 gr. were obtained from Basrah University laboratory animal house, Iraq. The animals were kept in standard conditions (23 ± 2 °C, 12 h light / dark cycle). Standard diet and water were given *ad libitum*. Rats were randomly divided into four groups (10 each). The first group received single daily oral dose of normal saline (vehicle) to serve as negative control. The second group was given simvastatin (10 mg/kg), as single oral dose. Hepatotoxicity was induced in animals of the third and fourth groups by a single oral dose of paracetamol 800 mg/kg. The third group of animals were treated

simultaneously with simvastatin (10 mg/kg), as a single daily oral dose. While the fourth group was given normal saline to serve as positive control. After 72 hours, the rats were anesthetized by diethyl ether; 5 ml of blood were taken by cardiac puncture. The abdomen was opened, and the livers were removed and cleaned. Liver tissue samples were fixed in 10% formalin solution and processed by routine histological technique for histopathology analysis.

The collected blood samples were allowed to clot. Sera were removed by centrifugation at 3000 rpm for 10 min. Then serum samples were processed to determine the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein and albumin, using a spectrophotometric autoanalyzer (Olympus AU-2700).

Results:

Paracetamol hepatotoxicity was associated with significant decrease in the serum total albumin (g/dl) $p<0.05$) and total protein(g/dl) ($p<0.05$). However, it significantly increased ($p< 0.0001$), ALT IU/L, AST IU/L, and ALP IU/L as shown in group 3 (positive control) in comparison with the negative control (group 1) (table 1). Using of simvastatin in healthy animals (group 2) caused slight insignificant changes in serum total albumin(g/dl), total protein(g/dl), ALT IU/L, AST IU/L, and ALP IU/L. However, simultaneous administration of simvastatin with paracetamol, significantly attenuate the adverse changes in the serum total albumin(g/dl), total protein(g/dl), ALT IU/L, AST IU/L, and ALP IU/L. However, it didn't bring them to the normal limits. Histopathological studies in hepatotoxicity induction untreated group showed that paracetamol caused pathological changes in liver consisted of congestions, hydropic degeneration and necrosis. In Simvastatin treated rats the liver sections were almost appeared in normal appearance with mild congestion, hydropic degeneration and necrosis.

Table 1: Effect of simvastatin on total albumin(g/dl), total protein(g/dl), ALT

Parameters Groups	Total albumin (g/dl)	Total protein (g/dl)	ALT IU/L	AST IU/L	ALP IU/L
Group 1 negative control (treated by saline without induction	5.21±0.91	6.44±1.22	33.41±3.34	38.81±2.96	112.81±6.83
Group2 (without induction and treated with simvastatin)	NS 5.01±0.81	NS 5.98±0.92	NS 34.21±3.29	NS 37.82±2.49	NS 114.85±5.93
Group3 positive control (induction and treated with saline)	p<0.05 3.75±0.72	p<0.05 4.62±0.88	p<0.0001 76.82±5.63	p<0.0001 81.82±6.23	p<0.0001 173.44±7.49
Group 4 (induction.and treated with simvastatin)	NS 4.12±0.75	NS 6.82±1.14	p<0.01 56.92±4.44	p<0.01 64.91±4.78	p<0.01 162.52±6.75

IU/L, AST IU/L, and ALP IU/L in paracetamol induced hepatotoxicity in rats

P value in comparison with positive control (group 1), NS : not significant,

II. DISCUSSION:

The liver is the key organ regulating homeostasis in the body. It is involved with almost all the biochemical pathways related to growth, fight against disease, nutrient supply, energy provision and reproduction. Paracetamol is commonly and widely used analgesic and antipyretic drug. It was safe when used in a therapeutic dose. It is detoxified mainly via formation of sulfate- and glucuronide-conjugates. When the enzymes saturated, paracetamol is increasingly metabolized into a reactive metabolite, Nacetyl-p-benzoquinone imine (NAPQI) by cytochrome P450 (CYP). The NAPQI is subsequently detoxified by glutathione (GSH) and the conjugated metabolite is excreted. When GSH is depleted, NAPQI is accumulated in the hepatocyte and interacts with thiol-containing proteins leading to hepatic necrosis . Paracetamol-induced liver injury is commonly used as models for investigation the efficacy of hepatoprotective drugs [55].

The elevated serum liver enzymes such as ALT, AST and ALP in intoxicated rats can be attributed to the damage in the histostructural integrity of the liver cells (hepatocytes) [56].

It has been documented that covalent binding of N-acetyl-p-benzoquinone imine, an oxidation product of paracetamol, to sulphydryl groups of protein resulted in cell necrosis and lipid peroxidation with concomitant decrease in glutathione levels in the liver [57-58]. In the assessment of liver damage by paracetamol, the determination of enzyme marker levels such as ALT and AST is often used. In necrosis or membrane damage, the enzymes are released into circulation and it can be therefore measured in serum as markers of hepatic damage. Elevated levels of serum enzymes are indicative of cellular leakage and loss of functional integrity of cell membrane in liver [59]. However, serum ALP and bilirubin level were also related to the function of hepatic cell.

Numerous studies suggest inhibitory effects of statins on proinflammatory cytokine production, such as IFN-γ, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6 in several cells, including microglia, astrocytes, and mononuclear cells. Accordingly, statins possessed many protective effects including neuro and pulmonary protection. They were reduce neutrophil influx which might have a strong effect on attenuating the downstream inflammatory events, such as macrophage influx, lymphocyte activation and inhibition of cytokine release [60-62]. The inhibition of IL-6, IL-8 and GM-CSF expression by statins has been shown in human cell cultures . Statins also affected IL-6 levels in the systemic circulation exert anti-oxidative effects and inhibit apoptosis [56-58]. Statins could conceivably affect these pathways through their inhibition of intracellular prenylation and inhibition of the GTP-binding proteins that underlie these inflammatory pathways [61-63]. Furthermore, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) protect the brain against ischemic injury by upregulating endothelial nitric oxide synthase (eNOS. Ischemic lesion volumes and neurologic deficits were significantly reduced in mice by both simvastatin and atorvastatin. Statins increased eNOS and tPA mRNA levels but did not change mRNA levels of PAI-1[64]. Therefore, the hepatoprotective effects of simvastatin could be attributed to its interference with many pro- and inflammatory mediators which preceded hepatotoxicity.

III. CONCLUSION:

According to the results of this study, simvastatin possessed hepatoprotective characterestics against paracetamol induced hepatotoxicicity.

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