EFFECT OF SOME CALCIUM CHANNEL BLOCKERS (NIFEDIPINE AND AMLODIPINE) ON THE INJURY ASSOCIATED TO HEPATIC ISCHEMIA-REPERFUSION IN ALBINO RATS

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ABSTRACT
Hepatic ischemia is an important factor in the development of hepatic degeneration and necrosis in different hepatic pathological conditions.

This study was conducted to declare the effect of pretreatment of albino rats with dihydropyridine L-type calcium channel blockers (nifedipine and amlodipine) on hepatic ischemia reperfusion (I/R). Furthermore this study investigated the effect of I/R on plasma levels of endothelin-1 (ET-1) and nitric oxide (NO) and their pathophysiologic links to maintenance of hepatic function.

This study was carried on 36 male albino rats. The animals were divided into 6 equal groups, each consisted of 6 rats. Group (1): sham operated (rats subjected to anesthesia and laparotomy). Group (II): control I/R rats, pre-treated with saline. Group (III): treated with nifedipine (2mg/kg/day) intra-gastric for 6 weeks before exposure to sham operation. Group (IV): I/R treated with nifedipine with the same previously mentioned dose and for the same duration before induction of I/R. Group (V): amlodipine pretreated (0.5mg/kg/day) for 6 weeks, intragastrically and then exposed to sham operation. Group (VI): received amlodipine 0.5mg/kg/day for 6 weeks before being subjected to I/R. Transient hepatic ischemia for 90 minutes was done under anesthesia by hepatic vascular pedicle clamping
followed by 30 minutes reperfusion. Hepatic cell function was tested by measuring plasma alanine transfe-
rase (ALT). This is in addition to measurements of hepatic tissue calcium content, plasma endothelin-1 and plasma nitrites. It was found that I/R produced a significant increase in plasma ALT, ET-1, nitrites and hepatic tissue calcium. Both nifedipine and amlodipine induced hepatoprotective effect confirmed by prevention of the elevation in plasma levels of ALT and hepatic tissue calcium load. Each of nifedipine and amlodipine had equally prevented the hepatic accumulation of calcium. In spite of this equipotent any of the drugs exerted significant changes in plasma ET-1 levels, while plasma nitrites levels remained high. Further studies of these results on hepatic patients are recommended especially in patients given nifedipine or amlodipine for associated cardiovascular problems.

INTRODUCTION

Hepatic ischemia occurs in hemodynamic and cardiogenic shock and interruption of hepatic blood flow can be necessary during extensive liver resection for trauma or tumors and in liver transplantation, during which re-
sections are frequently performed under complete or partial vascular occlusion to reduce blood loss and it has been shown that intermittent rather continuous pedicle occlusion leads to lower post-operative morbidity and mortality rates

Endothelin family (endothelin1, 2, 3) consists of 21 amino acid (3). Endothelin-1 (ET-1) is produced mainly by endothelial cells, vascular smooth muscle cells and to a lesser extent by hepatocytes. ET-2 is mainly produced within the kidney and intestine, whereas the highest levels of ET-3 are found in the brain (4). Endothelin receptors (ET_\text{A} & ET_\text{B}) are present in many internal organs, e.g. heart, adrenals, kidneys, lung tissue and central nervous system (5).

Liver has been considered to be a major organ that greatly alters its functions through mechanisms involving ET-1, one of the most potent vasoconstrictors produced by vascular endothelial cells. ETA receptor is predominantly expressed on vascular smooth muscle cells and executes vasoconstriction (7,8) on the other
hand, ETB receptor occurs in endothelial cells, Kupffer cells, and vascular smooth muscle cells and its stimulation in endothelial cell induces nitric oxide (NO) mediated vaso-relaxation through activation of constitutive NO synthase (9,10). The factors stimulate endothelin production by endothelial cells include mechanical stimulations of the endothelium, thrombin, calcium ions, epinephrine, angiotensin II, vasopressin, dopamine, erythropoietin, cytokines as IL-1, insulin-like growth transforming factor beta, endotoxins and lipids (low density lipoproteins and high density lipoproteins). The substances inhibiting endothelin synthesis are NO, cyclic guanosine monophosphate (cGMP), atrial natriuretic peptide (ANP), prostacyclin (PGI2) and bradykinins (4). Although circulating endothelin levels may not fully reflect local vascular production because more than two thirds of endothelin is released abuminally (11), elevated plasma endothelin levels may indicate overproduction of the peptide. Elevated endothelin plasma levels have been described in atherosclerosis (12,13) and other cardiovascular diseases such as stroke, pulmonary hypertension, cardiogenic shock and congestive heart failure (14,15,16). Importantly plasma endothelin levels after acute myocardial infarction are elevated and correlate with the severity of the disease (13,14). In addition to vasoconstriction, it might also promote vascular cell proliferation in atherosclerosis with consecutive narrowing of the vessels, especially in situations with enhanced endothelin release and thus further deteriorate organ perfusion and oxygen supply.

Calcium channel entry blockers (CCEBs) are drugs extensively used in cardiology practice. CCEBs include a broad spectrum of various drugs with different actions on the heart and the vessels (17). Three groups of routinely used CCEB, the high voltage (L-type) calcium channel have been accepted phenylalkylamines (e.g. verapamil), dihydropyridines (nifedipine, nimodipine, amlodipine) and benzothiazepines (e.g. diltiazem). Clevidine is another IV group of 1, 4 dihydropyridine with ultrashort activity, being rapidly hydrolyzed by esterases (18, 19). The first generation dihydropyridine L-type CCBs, such as nifedipine, were developed as selective and
powerful vasodilator \((20, 21)\). To increase the selectivity of nifedipine, a series of 2nd generation CCEB e.g nimodipine was developed by altering nifedipine’s physicochemical and pharmacodynamic properties \((22)\). A third generation series of L-type CCBs has also been developed and at least one of these, amlodipine \((23)\). It is very likely that part of the difference between amlodipine and nifedipine stems from the unexpected property of amlodipine to release NO \((24)\).

The aim of the present work is to study the effect of pre-treatment with dihydropyridine L-type calcium channel blockers (nifedipine and amlodipine) on hepatic ischemia-reperfusion \((I/R)\) induced injury in albino rats. In addition the purpose of this study was to examine the effects of \(I/R\) on plasma levels of ET-1 and its pathophysiologic links to maintenance of hepatic functions.

**MATERIALS & METHODS**

**Animals used:**

This experiment was carried on 36 male albino rats, weighing 220-260 grams/rat. Animals were having free access to water & food. They were exposed to similar housing conditions of heat & humidity.

**Drugs used:**

- Nifedipine (Epilat capsules): 10 mg, supplied by Epico-Co.
- Amlodipine (Norvasc tablets): 5 mg, supplied by Pfizer-Co.

**Animals grouping:**

The animals were divided into 6 equal groups, each consisted of 6 rats.

**Group (1):** Sham operated (anesthesia + laparotomy) but without hilum clamping of the hepatic vascular pedicle. This group pretreated with intragastric saline, 0.5 ml/kg/day for 6 weeks.

**Group (2):** Control group (anesthesia + ischemia reperfusion; \(I/R\)). These animals pretreated with saline in the previous amount and duration and subjected to 90 minutes hepatic ischemia induced by hilum clamping of hepatic vascular pedicle, followed by 30 minutes of reperfusion.

**Group (3):** Pretreated with intragas-
tric nifedipine in a dose of (2 mg/kg/day) for 6 weeks and then exposed to sham operation (25).

Group (4): I/R pretreated with nifedipine in a dose of 2 mg/kg/day, intragastrically for 6 weeks (25).

Group (5): Pretreated with amlodipine 0.5 mg/kg/day intragastrically for 6 successive weeks and exposed to sham operation (26).

Group (6): Rats with induced I/R and pretreated with amlodipine (0.5 mg/kg/day), intragastrically for 6 weeks (26).

Surgical procedures:
Liver ischemia was induced according to the method of Nauta et al. and Peralta et al. (6, 27). Hepatic ischemia was performed under general anesthesia one hour after the last drug dose. Sodium thiopental (the used anesthetic agent) was given in a dose of 30 mg/kg body weight intraperitoneally (IP) for induction and repeated when required in a dose of 10 mg/kg, IP for maintenance (27). After section of the ligaments of the liver, hepatic ischemia was induced for 90 minutes by hilum clamping of hepatic vascular pedicle using bulldog clamp. During the period of ischemia, 0.5 ml of saline was given IP every 30 minutes to maintain hemodynamic stability. Reperfusion was established by removal of the clamp. After 30 minutes of reperfusion, the animals were killed by knifing and their livers were immediately removed for assay of hepatic calcium content. In addition, blood was collected for estimation of plasma alanine amino transaminase (ALT), endothelin and nitric oxide (nitrites).

Estimation of ALT:
ALT activity was determined by enzymatic technique (28) using Biotic laboratories kits. The activity was expressed as units/liter.

MEASUREMENT OF NITRIC OXIDE
This is done by measuring nitrite (NO₂) which is one of two primary stable and non-volatile breakdown products of NO This method is in accord to Griess et al: (29) and Breddt and Snyder (30). Nitrites, a stable oxidation product of NO are measured by a spectrophotometer assay using the Griess reagents, sulfanilamide,
HCl and N- (1-naphyl) ethylenediamine (NED).

**Measurement of plasma immunoreactive endothelin-1 (irET-1):**

It was determined according to Rubanyi et al & Gian et al. (31& 32). Plasma samples were drawn into chilled EDTA tubes (1mg/ml blood) containing aprotonin (500 KIU/ml of blood). Centrifuge the blood at 1.600 xg for 15 minutes at 0°C. Stored at -70°C until the time of assay.

**Measurements of hepatic calcium tissue:**

At the end of the 30 minutes of reperfusion, the hepatic tissue calcium load was measured using Perkin-Elmer 22380 atomic absorption spectrophotometer with air acetylene flame. Its value was expressed in mg/gm liver tissue (33).

**Statistics:**

Student's t-test according to Pippins (34) was used to compare statistically significant changes between control groups and test groups. P value = or< 0.05 was considered to be significant.

**RESULTS**

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A significant increase in liver enzyme (ALT) and hepatic tissue calcium contents (from 12.1±0.3 & 0.09 ± 0.002 to 24 ± 0.4 & 0.99 ± 0.002, respectively) were observed in the group subjected to ischemia reperfusion as compared to the control group (Tab. 1). In addition I/R induced a significant increase in both plasma levels of ET-1 and nitrites (from 5.1 ± 1 and 21.7+1.1 to 9.3 ± 0.2 and 29.8 +0.9) respectively in comparison to sham operated group (tab2 & Fig 1). When ischemia was preceded by nifedipine administration to the rats in a dose of 2 mg/kg/day intragastrically for 6 weeks, the elevation in plasma ALT and hepatic calcium levels were prevented (table 1). Also when I/R was preceded by administration of amlodipine to the rats in a dose of 0.5 mg/kg/day intragastrically for 6 weeks, the increase in plasma ALT & hepatic tissue calcium levels were prevented (Tab.1)

In addition nifedipine pretreatment induced a non significant changes in plasma immunoreactive endothelium-1 (irET-1) levels accompanied by increase in plasma nitrites in comparison to I/R control groups (from 9.3
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±0.2 to 8.9 ±0.7 for ir ET-1 and from 29.8 ± 0.9 to 37.2 ±3.3 for nitrites,
Tab. 2 & Fig. 1)

Also, amlodipine pretreatment in-
duced non-significant changes in plasma ir ET-1 levels (from 9.3 ± 0.2
to 9.1± 0.8) accompanied by increase in plasma nitrites (from 29.8 ± 0.9 to 50.8 ± 2.1) as showed in (tab. 2 & Fig.1).

Table (1): Effect of intragastric pretreatment by either nifedipine ( 2 mg/kg/day) or amlodipine ( 0.5 mg/kg/day) for 6 weeks on plasma ALT and on hepatic tissue calcium content in hepatic ischemia reperfusion (I/R) injury in rats (Mean ± SE).

<table>
<thead>
<tr>
<th>Groups</th>
<th>N = 6</th>
<th>Group (1) Sham-operated (Anesthesia I laparotomy)</th>
<th>Group (2) Control IR</th>
<th>Group (3) Sham I nifedipine</th>
<th>Group (4) IR I nifedipine</th>
<th>Group (5) Sham I amlodipine</th>
<th>Group (6) IR I amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ALT (IU/L)</td>
<td></td>
<td>12.1 ± 0.3</td>
<td>24 ± 0.4*</td>
<td>12.1 ± 0.3</td>
<td>14.5 ± 1.1*</td>
<td>12.2 ± 0.2</td>
<td>13.5 ± 0.9*</td>
</tr>
<tr>
<td>Hepatic tissue calcium</td>
<td></td>
<td>0.099 ± 0.002</td>
<td>0.99 ± 0.002*</td>
<td>0.099 ± 0.003</td>
<td>0.09 ± 0.004*</td>
<td>0.089 ± 0.005</td>
<td>0.08 ± 0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(mg/gm liver tissue)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SE = standard error.

ALT = alanine transaminase

* = Significant difference between control I/R and sham operated group.

*= Significant difference between I/R drug pre- treated (amlodipine or nifedipine) and I/R control group.

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Table (2): Effect of intragastric pretreatment by either nifedipine (2 mg/kg/day) or amlodipine (0.5 mg/kg/day) for 6 weeks on plasma levels of endothelin-1 like immunoreactivity (ir ET-1) and nitrites in rats with induced hepatic I/R (mean ± SE).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group (3)</th>
<th>Group (4)</th>
<th>Group (5)</th>
<th>Group (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 6</td>
<td>Sham-operated (Anesthesia + laparotomy)</td>
<td>Control IR</td>
<td>Sham + nifedipine</td>
<td>IR + nifedipine</td>
<td>Sham + amlodipine</td>
<td>IR + amlodipine</td>
</tr>
<tr>
<td>Plasma irET-1 pg/ml</td>
<td>5.1 ± 0.1</td>
<td>9.3 ± 0.2*</td>
<td>5.2 ± 0.3</td>
<td>8.9 ± 0.7</td>
<td>4.9 ± 0.2</td>
<td>9.1 ± 0.8</td>
</tr>
<tr>
<td>Plasma nitrites (µmol/L)</td>
<td>21.7 ± 1.1</td>
<td>29.8 ± 0.9*</td>
<td>21.9 ± 0.3</td>
<td>37.2 ± 3.3*</td>
<td>22.1 ± 0.8</td>
<td>50.8 ± 2.1*</td>
</tr>
</tbody>
</table>

SE = standard error.
ALT = alanine transaminase
* = Significant difference between control I/R & sham operated group.
** = Significant difference between I/R and drug pre-treated (amlodipine or nifedipine) and I/R control group.
Fig (1): Effect of intra-gastric pretreatment by either amlodipine (0.5 mg/kg/day) for 6 weeks or nifedipine (2 mg/kg/day) for 6 weeks on plasma levels of endothelin-1 like immuno reactivity (ir ET-1) and nitrites in rats with induced hepatic I/R (mean ± SE).

SE = standard error.
ALT = alanine transaminase.
* = Significant difference between control I/R & sham operated groups.
* = significant difference between I/R drug pre-treated (amlodipine or nifedipine) and I/R control groups.
DISCUSSION

Liver cell injury is a common event in clinical practice. Ischemia reperfusion injury considered of the most important causes of liver cell injuries. A number of surgical maneuvers require a period of liver ischemia, on reperfusion hepatic injury results from failure of the microcirculation and excessive inflammatory responses. Furthermore, anoxic liver injury occurs during organ preservation for liver transplantation as a treatment of end stage of liver disease. Therefore, in the present work model of I/R was chosen due to its important clinical relevance.

In the present study, rat groups subjected to I/R showed significant hepatic function alternations demonstrated by increase in plasma levels of ALT. There were also significant increases in hepatic tissue calcium levels. These findings are in accord with previous studies. They reported that interference with Ca+2 homeostasis and increased levels of cytoplasmic free calcium participate in cell injury through disruption of cellular thiol homeostasis. Certain proteins are highly sensitive to changes in the thiol status, including Ca2+-dependent adenosine triphosphate which serves as membrane bound Ca2+ pumps to the ion that maintain cytoplasmic calcium at low levels. A sustained elevation in cytoplasmic Ca2+ may mediate adverse effects on cellular viability via activation of endonucleases and phospholipases as well as enhanced production and accumulation of free radicals. This can lead to a chain of reactions involving lipid peroxidation eventually resulting in membrane damage and alternations of membrane bound protein function including the Ca2+-ATPase. Furthermore, I/R provoked a significant increase in plasma endothelin-1 and nitrites. These results supported by the study of Taniani et al., as they found that during anoxia re-oxygenation, plasma ET-1 levels were elevated and blockade of its effect by endothelin antagonists attenuated reperfusion injury, suggesting deteriorating effects of this vasoconstrictor peptide on hepato-portal hemodynamics. Mechanism by which ET-1 aggravates the hepatic reperfusion injury has been thought to involve impairment of sinusoidal patency through its vasoconstrictor actions.
This notation was supported by previous studies showed that trans-portal administration of ET-1 induced a marked vasoconstriction at portal venules and a reduction of bile flow. The increase in plasma nitrites levels associated with I/R could be explained on the light of Tanian et al study, where they reported that ET-1 is released during the early period of re-oxygenation and stimulates ETB receptors-mediated signaling to trigger NO-dependent and independent mechanisms. Despite markedly different chemical structure, all compounds of the three main classes of Ca^{2+} antagonists (dihydropyridines, phenylalkylamines and benzothiazepines) inhibit the inward flow of Ca^{2+} ions through (L-type) calcium channels. However, because of binding at different receptor sites, different pharmacokinetic properties, and different effects at the levels of the cardiovascular (coronary and peripheral arteries, cardiac conduction system and myocardium) and extracardiovascular systems, each of these compounds has its own advantages and disadvantages. For these reasons two members of calcium channel antagonists were used in the present study to evaluate any possible differences in their effects on I/R.

Pretreatment of rats with nifedipine before induction of ischemia-reperfusion produced a significant decrease in hepatic calcium contents, plasma ALT and plasma ET-1 with significant increase in plasma nitrites level as compared to I/R control group. These finding are in agreement with Goto et al, and Sogni et al. They reported that nifedipine could prevent the incidence of halothane induced hepatotoxicity by preventing the increase in cytosolic calcium concentrations. Moreover, in vitro study revealed that nifedipine pretreatment exhibited a preventive effect against acetaminophen-induced hepatocytes injury by keeping intracellular calcium levels within the normal control values. Using the isolated rat hepatocyte exposed to ethanol, Coberes et al. observed a significant decrease in ALT and lipid peroxidation after nifedipine treatment. The present study extends these findings to in vivo model. Although several NO synthase isoforms
have been isolated all are homologous and divided into two categories with different regulations and activities. The constitutive isoforms in neuronal and endothelial cells are always present (49). These NO synthase isoforms are inactive until intracellular Ca\textsuperscript{2+} levels increase, the Ca\textsuperscript{2+} binding level increase, the Ca\textsuperscript{2+} -binding protein calmodulin binds to Ca\textsuperscript{2+} and Ca\textsuperscript{2+} calmodulin complex binds to and activates NO synthase (49). The constitutive NO synthase isoforms then synthesize small amount of NO until intracellular Ca\textsuperscript{2+} levels decrease. In contrast, the inducible NO synthase isoform is normally not expressed in macrophages and hepatocytes when activated by specific cytokines these cells produce inducible NO synthase enzyme that synthesizes large amounts of NO. Although the inducible synthase is Ca\textsuperscript{2+} independent, the dihydropyridine Ca\textsuperscript{2+} -channel antagonist, nifedipine reduced bacterial lipopolysaccharide induced NO production in cultured macrophages (49). Thus, in certain preparations acute treatment with Ca\textsuperscript{2+} antagonists may directly stimulate NO release as well as facilitate the effects of NO at the level of vascular smooth muscle cells. It seems that at least part of the increased NO release by nifedipine is due to a protection from reactive oxygen species (ROS), which deactivates NO (50). However, chronic nifedipine therapy does not improve endothelial NO release in normotensive animals (51). The evidence of slow onset and long duration of action, suggested that amlodipine had pharmacological properties distinct from other calcium channel antagonists particularly nifedipine (52). In addition a number of studies have suggested that amlodipine inhibits platelet aggregation (53). Changes in shear stress are thought to be important in the regulation of NO production, whenever blood flow changes, so do shear and NO release (54). Therefore all vasoactive drugs have the potential to release NO because of the changes in physical forces that distort the endothelial cells. Amlodipine prompts the production of NO through the activation of eNOS. The effect on eNOS is apparently transduced via activation of angiotensin receptor followed by the generation of kinins & stimulation of the B\textsubscript{2}-kinin receptor (52). Amlodipine, unlike nifedipine or diltiazem, caused a dose
dependent release of nitrite, the hydration product of NO. The ability of amlodipine to release NO was unexpected, because: NOS is a calcium dependent enzyme and amlodipine should reduce intra-endothelial cell calcium and there are no L-type calcium channels on endothelial cells for amlodipine to block (52). Several studies have suggested that small vessels are more dependent on the influx of extra-cellular Ca$^{2+}$ than larger vessel (49). Furthermore, it has been shown that nifedipine strongly reduced contraction due to ET-1 in porcine ciliary arteries (55). This may also explain why, in the human microcirculation of normal subjects, intra-arterial administration of verapamil or nifedipine fully prevents ET-1 induced contractions (56). Interestingly calcium antagonists can reverse endothelin induced contraction in both the porcine coronary as well as the human internal mammary artery (57, 58).

The probable reason for this is that, in contracting cells, ET lowers the membrane potential of vascular smooth muscle cells (59) which led to opening voltage operated Ca$^{2+}$ channels. Therefore, once contractions have developed, Ca$^{2+}$ antagonists are able to exert an inhibitory effect. Although ET-1 was originally considered to be an endogenous activator of voltage-operated Ca$^{2+}$ channel (49), it has been shown that ET-1 interacts with specific receptors on vascular smooth muscle (ETA & ETB receptors) mediating vasoconstriction and proliferation. On endothelial cells, ET interacts with ETB receptors, stimulating the formation of NO and PGI2 (49). ETA receptors bind endothelin-1 and to a lesser degree, endothelin 3; ETB receptors bind endothelin -1 and endothelin 3 with similar affinity (60, 61).

Administration of amlodipine in a dose of 0.5 mg/kg/day for 6 weeks to rats before induction of I/R produced a non-significant changes in plasma ET-1. In contrast to this study, Inigo et al. (61) found that ET-1 concentrations were significantly higher during amlodipine compared with losartan treatment in crossover trial in renal transplant recipients. Furthermore, in vitro study reported that amlodipine at high dose (20 mg/kg/day) increased preproendothelin-1 expression in rat
ventricles and aorta of normotensive rats because this dose can activate the sympathetic nervous systems and the rennin angiotensin system. Both nor-adrenaline and angiotensin II stimulate preproendothelin-1 gene expression (62). However, amlodipine attenuates the ischemia and reperfusion-induced increase in cardiac ET-1 binding sites in hearts from rats pretreated with amlodipine (0.25-0.5 mg/kg) (63). In addition in a human study, twenty and forty minutes ischemia caused a time dependent increase in ET-1 binding density. Amlodipine pretreatment attenuated this increase in a time and dose dependent manner. Amlodipine (0.25-0.5 mg/kg) also suppressed the ischemia induced increase in ET-1 binding site density (64).

In conclusion both nifedipine and amlodipine exerted a protective effect against the injury associated to hepatic ischemia reperfusion in rats. Six weeks of therapy with nifedipine or amlodipine improves liver function by increasing the bioavailability of nitric oxide (this increase of NO levels was higher in groups treated with amlodipine than in that treated with nifedi-

pine ) and by preventing the increase of hepatic calcium content that occurred with I/R injury.

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المخصص العربي

تأثير بعض قنوات الكالسيوم (النيفيديبين والأملوديبين) على الإصابة التي تحدث في كبد الفئران البيضاء نتيجة تعرضها لقصور في الدورة الدموية بالكبد ثم إعادة ضخ الدم.

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يعتبر القصور في الدورة الدموية للكبد عاملاً مهماً في حدوث وتطور الضمور وكذلك الموت للخلايا الكبدية في مختلف حالات أمراض الكبد.

أجري هذا البحث لدراسة احتمال وجود تأثير وقائي لكل من عقارى النيفيديبين والأملوديبين على الإصابة التي تحدث في الكبد نتيجة لقصور في الدورة الدموية به استعادة وصول الدم بعد فترة.

تم إجراء هذا البحث على 36 فئراً أبيضًا من الذكور السليمة صحياً بووزن يتراوح من 20 إلى 25 جرام. قسمت الفئران البضاء إلى 6 مجموعات متساوية.

ال مجموعة الأولى: قياسية (لم تعرض إلى قصور في الدورة الدموية الكبدية).

ال مجموعة الثانية: قياسية (عرضت لقصور في الدورة الدموية الكبدية).

ال مجموعة الثالثة: معالجة بداء النيفيديبين بجرعة 2 مجم/كمجم يومياً لمدة 6 أسابيع متتالية.

 ولم تعرض لقصور في الدورة الدموية الكبدية.

ال مجموعة الرابعة: معالجة بالنيفيديبين بنفس الجرعة وتنفس المدة السابقة ذكرها ولكنها عرضت إلى قصور في الدورة الدموية الكبدية بعد العلاج.

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المجموعة الخامسة: معالجة بدواء الأملوديبين بجرعة 0.5 مجم/كجم يوميا لمدة 6 أسابيع متناولة بينما لم يتم تعرضها إلى قصور في الدورة الكبدية).

المجموعة السادسة: مثل الساقية ولكنها عرضت إلى قصور في الدورة الدموية لمدة 10 دقائق ثم إعادة ضغ الدم لمدة 30 دقيقة.

أحد القصور الدموي الكبدى في الفئران المحضرة بفتق الحزمة الوعائية الدموية الداخلية للخليقة لمدة 20 دقيقة متبوعة بفترة 30 دقيقة إعادة للدموع وذلك برفع الفلق عن الحزمة.

اختبرت وظيفة الخلايا الكبدية بقياس مستوى نزيف الأدينين أمينوترينانسفيراز في البلازما وقياس درجة تراكم الكالسيوم بالنسيج الكبدى وقياس كل من مستوى الأندوثيلين - 1 وكذلك مستوى النيتربيدات في البلازما.

في هذا النموذج التجريبي أشارت النتائج إلى زيادة مستوى نزيف الأدينين أمينوترينانسفيراز في البلازما وكذلك زيادة كل من كمية الكالسيوم في الأنسجة الكبدية ومستوى الأندوثيلين - 1 وأيضاً مستوي النيتربيدات في البلازما كما وجد أنه لكل من دوالي البنفسجيين والأملوديبين تأثير متساوي في حماية الكبد من الإصابة بقصور الدورة الدموية الكبدية وتوضح ذلك إزاحة مستويان من الانزيمات في البلازما وكذلك كمية الكالسيوم في الأنسجة الكبدية.

وبالرغم من هذا التأثير الإيجابى الملحوظ فلم يحدث أي من تغيير ذو دلالة إحصائية في مستوى الأندوثيلين - 1 في البلازما، بينما ظل مستوي النيتربيدات في البلازما مرتفعاً وكان أكثر ارتفاعاً مع دواء الأملوديبين، وعلى ضوء هذا البحث نوصي بدراسة هذه الآثار في مرضى الكبد وخصوصاً في المرضى الذين يتناوليون هذه الأدوية لأعراض أخرى مثل مشكلات قصور وظائف الجهاز الدوائي والقلب.

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