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Effects of adenosine and dipyridamole on serum levels of some biochemical markers in rabbits: Running title: Biochemical effects of adenosine and dipyridamole

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ABSTRACT

Adenosine is a nucleoside which occurs naturally in a diverse forms in all cells of the body and in most biological fluids. Under basal conditions, the extracellular adenosine concentration is maintained within certain limits. Dipyridamol inhibits adenosine reuptake by erythrocytes, endothelial cells and platelet increasing plasma levels of adenosine Aims: study the effects of adenosine and dipyridamole on serum levels of serum urea, creatinine, alkaline phosphatase(ALP), lactate dehydrogenase (LDH), Aspartate Aminotransferase (GOT), and Alanine Aminotransferase (GPT). Material and methods: Thirty-five male rabbits were included in the study. The animals were divided into 3 groups: Group one(5 animals): injected intraperitoneal (i.p) with 2 ml of distilled water/day (control group). Group two (15 animals): were treated by i.p injection of adenosine, they were divided into 3 sub groups (5 animals) according to adenosine dose:1 mg/kg, 2mg/kg and 4 mg/kg.Group 3 (15 animals): were treated by dipyridamole orally, they were divided into 3 sub-groups (5 animals) according to dipyridamole dose:4 mg/kg, 8 mg/kg and 12 mg/kg. Result: Significant differences among 3 groups were found in blood urea, LDH, GOT levels, and in GPT levels. While statistical analysis of serum levels of S. creatinine and ALP showed no significant differences among 3 study groups. Conclusion: both adenosine, dipyridamole cause Significant differences among 3 groups were found in blood urea, LDH, GOT levels, and in GPT levels in rabbit

Introduction

It is well recognized that adenosine acts to restore energy balance in cells during exposure to stress or trauma. It has protective effects in a wide spectrum of normal physiological and abnormal pathological conditions including inflammation, neuronal hyper excitability, various toxicities, seizures, and pain. These protective functions of adenosine result in its classification as a "retaliatory" or "homeostatic" cellular modulator. Much facts have been accumulated on anti-inflammatory effects of adenosine molecule that is mainly mediated by A2a receptor activation; this receptor has an important role in matrix deposition and wound healing in a damaged tissue, and acting as a guard to mucosal and dermal tissues serving in protection and repair. Adenosine is a nucleoside which occurs naturally in a diverse forms in all cells of the body [1]. Adenosine derivatives are commonly found in nature and has a significant position in biochemical processes. Adenosine thiphosphate (ATP) and adenosine diphosphate (ADP) acting on energy transfer while cyclic adenosine monophosphate (cAMP) has a role in signal transduction. Also adenosine itself is a neuromodulator substance, supposed to have a major role in sleep promotion and arousal suppression. Adenosine also has an action on regulation of blood flow to a variety of organs throughout vasodilation. All these functions and others need specific signal through adenosine receptors.

Dipyridamole was introduced as a coronary vasodilator, given orally [2]. It inhibits the enzyme phosphodiesterass due to decrease of the adenosine transporter and elevates cAMP and eGMP levels. [3],[4]. Studies suggest that dipridamol gives good

useful direct and indirect action into the vasculature, including the endothelium including inhibition of proliferation, antioxidant, and anti-inflammatory properties [5]. Dipyridamol inhibits adenosine reuptake by erythrocytes, endothelial cells and platelet increasing plasma levels of adenosine [6]. This vasodilator activity of dipyridamole leads to improved tissue perfusion [7].

Materials and methods

Thirty five apparently local healthy mature male rabbits of (10-12) months old and body weight of 1.0-1.5 Kg were involved in the study. Animals were housed in animal house of college of Dentistry / University of Mosul.

Dose calculations

According to references, both adenosine((MACKLIN CAS: 58-61-7/CHINA) in powder form with a capacity of (25g) and with a concentration of (99.5%) and molecular weight (267.24) and Dipyridamole (tablet (75mg), European origin (CYPRUS) are mainstay drugs used for treatment of human diseases at a wide range of dosing intervals depending on patient condition and type of drug combined with them to produce effect[8] They are available mainly at 6mg, 12mg and 30mg for adenosine and 25mg, 50mg and 75mg for Dipyridamole.[9,10,11]. In this study the doses of rabbit were calculated according to human Equivalent doses using the following formula: animal dose (mg/kg) = human dose (mg/kg) x conversion factor(3.08 for rabbit) [12]. According to our experimental protocol, a pilot study was carried out using rabbit doses that result from conversion of human doses (t.i.d. /for adult human of 60 kg body weight) [13, 14], doses results from this calculation were 0.924, 1.848 and 4.620 mg/kg for adenosine, and 3.85, 7.70 and 11.55 mg/kg for Dipyridamole. After that we use up and down method on these calculated doses to find the doses that start to produce biochemical changes in serum examined which are 1, 2, and 4 mg/kg/day for adenosine and 4, 8 and 12 mg/kg/day for Dipyridamole which were also chosen because their uppermost safety limit [14,15,16,17]

Experimental design

The animals were randomly divided into 3 groups: Group one(5 animals): was injected (i.p) with 2 ml of distilled water per day throughout the trial period. (control group). Group two (15 animals): were treated by intraperitoneal injection of adenosine, they were divided into 3 sub groups (5 animals) according to adenosine dose:1 mg/kg, 2mg/kg and 4 mg/kg. Group 3 (15 animals): were treated by dipyridamole orally by gavage tube, they were divided into 3 sub groups (5 animals) according to dipyridamole dose: 4 mg/kg, 8 mg/kg and 12 mg/kg. All these groups were received their treatments once daily for 30 days.

Blood samples collection

Fresh blood was drawn from each rabbit for the analysis of biochemical parameters including serum levels of serum urea, creatinine, alkaline phosphatase, LDH, GOT, and GPT. Samples were collected after animals starvation for 12 hr. before blood sampling, then the serum was then separated by centrifuge (Volker's optical Gmll, Germany), and stored at (-20C°) till analysis by using Assay kits.

Results

Table (1) showing that comparison of liver and kidney function tests among adenosine, dipyridamole and control groups. Significant differences among 3 groups were found in blood urea levels (37.93±7.28, 60.86 ±6.14 and 73.00±2.69) mg/dl respectively, in LDH levels (137.54±28.11, 190.20±23.07 and 97.28±7.77)IU/L respectively, in GOT levels (19.44±17.12, 16.06±3.25 and 1.49±1.28)IU/L respectively, and in GPT levels (14.91±2.16, 36.25±7.57 and 23.30±3.19) IU/L respectively (Figures 1,2,3, and 4)

Table 1: Comparison in serum levels of liver & kidney function tests among the study sampled groups

Parameters	Group A mean ± SD	Group D mean ± SD	Control group mean ± SD	p-value*
No. of rabbits	15	15	5	---
B.Urea (mg/dl)	37.93 ± 7.28^{C}	60.86 ± 6.14^{B}	73.00 ± 2.69^{A}	0.000
S.creatinin (mg/dl)	1.70 ± 0.53^{A}	1.71 ± 0.39^{A}	1.18 ± 0.08^{A}	0.058
Alkaline Ph (IU/L)	21.38 ± 6.48^{A}	16.67 ± 9.36^{A}	17.32 ± 0.34^{A}	0.223
LDH (IU/L)	137.54 ± 28.11^{B}	190.20 ± 23.07^{B}	97.28 ± 7.77^{C}	0.000
GOT (IU/L)	19.44 ± 17.12^{A}	16.06 ± 3.25^{AB}	1.49 ± 1.28^{B}	0.018
GPT (IU/L)	14.91 ± 2.16^{C}	36.25 ± 7.57^{A}	23.30 ± 3.19^{B}	0.000

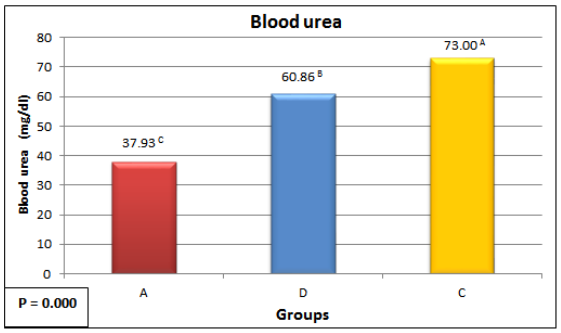

Fig. 1: comparison in mean blood urea level among adenosine, dipyridamole and control groups

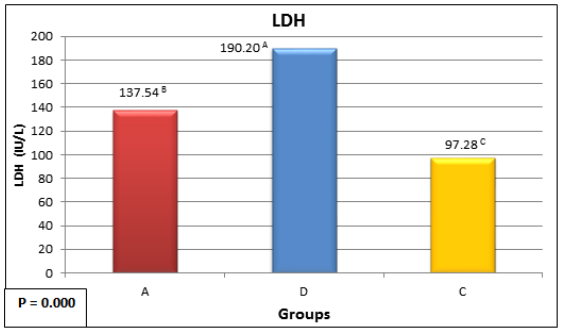

Fig. 2: comparison in mean LDH level among adenosine, dipyridamole and control groups.

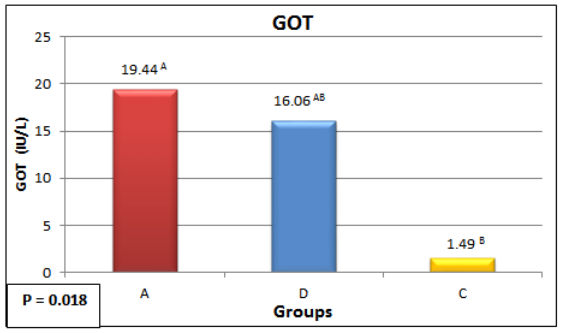

Fig. 3: comparison in mean GOT level among adenosine, dipyridamole and control groups.

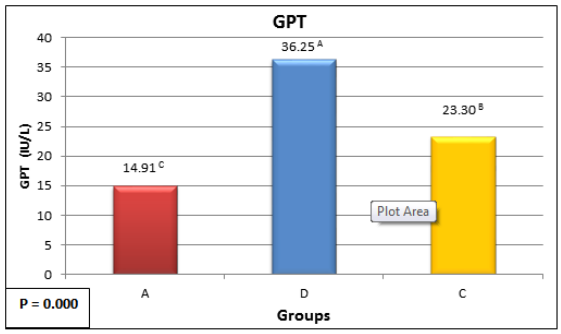

Fig. 4: Comparison in mean GPT level among adenosine, dipyridamole and control.

While statistical analysis of serum levels of S. creatinin, (1.70 ± 0.53, 1.71±0.39 and 1.18±0.08) mg/dl respectively, and alkaline phosphatase (21.38±6.48, 16.67±9.36 and 17.32±0.34) IU/L respectively, showed no significant differences among 3 study groups. (Figure 5 and 6).

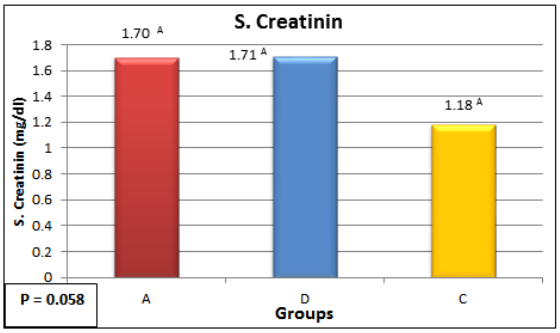

Fig. 5: comparison in mean S. creatinine among adenosine, dipyridamole and control groups.

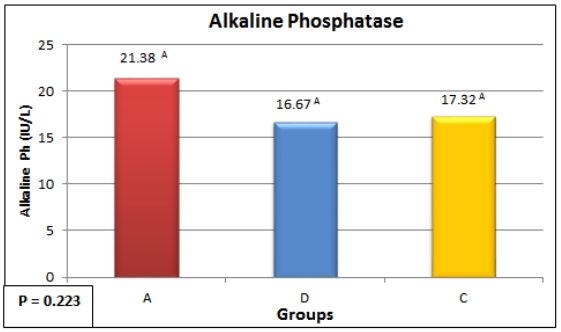

Fig. 6: comparison in mean alkaline phosphatase among adenosine, dipyridamole and control groups

In comparison of serum biochemical markers among adenosine groups and control group, highly significant differences among 4 groups were found in TAC levels (3.63±1.03 , 4.67±1.60, 7.14±0.25 and 13.33±2.50, 12.63±1.85, 16.93 ± 0.67 and 0.00 ± 0.00) u/ml respectively , in ADA (10.03±0.60, 12.63±1.85, 16.93±0.67 and 0.00±0.00U/mel respectively, in IL-6 levels (15.81±0.54, 15.23±0.49, 15.06 ±0.13 and 15.62 ± 0.01) pg/ml respectively and in GSH levels (22.97 ± 1.66, 23.56± 2.22, 19.80±3.07 and 5.54 ± 0.23) µg/ml respectively.

While statistical analysis of serum levels of TNF-α (15.89 ±0.80 , 15.35±0.52, 15.53± 0.29 and 15.63 ±0.03) pg/ml respectively showed no significant differences among 4 study groups (Table 2).

Table 2: the effect of different doses of adenosine on the liver and kidney function tests in group A and control group.

Parameters	Dosages in group A [adenosine]			Control group	P- value*
	1mg/kg Mean ± SD	2mg/kg Mean ± SD	4 mg/kg Mean ±SD		
No. of rabbits	5	5	5	5	---
B.Urea (mg/dI)	43.64 ± 9.35^{B}	35.67 ± 5.68^{B}	34.48 ± 1.98^{B}	73.00 ± 2.69^{A}	0.000
S.creatinin (mg/dl)	1.18 ± 0.46^{B}	1.78 ± 0.41^{A}	2.14 ± 0.17^{A}	1.18 ± 0.08^{B}	0.000
Alkaline Ph (IL/L)	24.31 ± 3.31^{A}	26.07 ± 3.10^{A}	13.75 ± 3.90^{B}	17.32 ± 0.34^{B}	0.000
LDH(IU/L)	117.38 ± 7.57^{BC}	134.38 ± 8.77^{AB}	160.90 ± 37.80^{A}	97.28 ± 7.77^{C}	0.001
GOT (IU/L)	42.62 ± 2.14^{A}	8.61 ± 0.92^{B}	7.09 ± 3.44^{B}	1.49 ± 1.28^{C}	0.000
GPR (IU/L)	13.35 ± 1.36^{B}	17.01 ± 0.54^{B}	14.38 ± 2.28^{B}	23.30 ± 3.19^{A}	0.000

• One-way ANOVA-test with Tukey's pair wise comparisons was used. Means that do not share a letter are significantly different.

In comparison of serum biochemical markers among dipyridamole groups and control group, highly significant differences were found in TAC levels (3.46±0.41, 3.38±0.30, 4.35±1.04 and 13.33±2.50) u/ml respectively , in ADA levels (25.38±3.58, 19.83±4.00, 24.13±2.64 and 0.00± 0.00) u/ml respectively, in GSH levels (9.14±1.89, 6.96±2.16, 4.89±0.40 and 5.54±0.23) µg/ml respectively. While statistical analysis of serum levels of TNF-α (16.09±1.14, 15.14±0.46, 15.23±0.39 and 15.63±0.03) pg/ml respectively and in IL-6 levels (15.59±0.07, 15.08±0.86, 15.49±0.16 and 15.62±0.01) pg/ml respectively, showed no significant differences among 4 study groups (Table 3).

Table 3: The effect of different doses of dipyridamole on the liver and kidney function tests in subgroups D and control group.

Parameters	Dosages in group D dipyridamole			Control group	P- value*
	4mg/kg Mean ± SD	8mg/kg Mean ± SD	12 mg/kg Mean ±SD		
No. of rabbits	5	5	5	5	---
B.Urea (mg/dI)	60.98 ± 7.02^{B}	63.81 ± 6.98^{AB}	57.80 ± 3.34^{B}	73.00 ± 2.69^{A}	0.003
S.creatinin (mg/dl)	1.66 ± 0.29^{A}	1.72 ± 0.34^{A}	1.76 ± 0.57^{A}	1.18 ± 0.08^{A}	0.0777
Alkaline Ph (IU/L)	25.97 ± 6.37^{A}	18.02 ± 3.28^{B}	6.01 ± 1.66^{C}	17.32 ± 0.34^{B}	0.000
LDH (IU/L)	208.61 ± 16.14^{A}	186.09 ± 6.33^{AB}	175.9 ± 29.30^{B}	97.28 ± 7.77^{C}	0.000
GOT(IU/L)	16.13 ± 2.75^{A}	17.82 ± 2.23^{A}	14.23 ± 4.03^{A}	1.49 ± 1.28^{B}	0.000
GPT(IU/L)	44.04 ± 0.65^{A}	36.40 ± 2.21^{B}	28.31 ± 3.19^{C}	23.30 ± 3.19^{C}	0.000

• One-way ANOVA-test with Tukey's pair wise comparisons was used. Means that do not share a letter are significantly different.

Discussion

Urea, commonly referred to as blood urea nitrogen (BUN), is the product of protein synthesis when measured in the blood. Therefore, the concentration to of urea depends on protein intake, the ability of the body to metabolize protein, and sufficient excretion of urea by the renal system. Amonia is then converted to urea by liver enzyme- [18] . It is almost entirely expelled from the body by the urinary kidneys [19] . In the present study, the control group observed a substantial rise in the amount of urea in the blood serum after 30 days of the experiment in comparison with adenosine and dipyridamole groups.The value of urea as a test of renal function could depends on the GFR, as GFR decreases, serum urea increases. On other hand, urea can be elevated despite regular GFR (i.e. normal renal function). So that urea loses specificity as a sign of renal function [20, 21]. Studies indicated that health individuals could have BUN levels as high as 40-50 mg/dl (14.3- 17.8 mmol/L) (without any apparent loss of renal function). [22,23] The findings of our current study disagree with the results of Taskiran [24] et al., 2016, where adenosine treatment has been found to significantly attenuate nephropathy and improve renal dysfunction, as evidenced by decreased plasma levels of urea, creatinine and kidney injury molecules- 1 (KIM-1) levels.

Dipyridamole was associated with a low rate of serum enzyme elevation [25]. This is compliant with our existing results of urea. Our analysis also agreed with the [26] report which stated that the elevated level of serum urea in gentamicin- administered rats was significantly reduced by both dipyridamol pre-treatment and post- treatment, but dipyridamol pre-treatment showed slightly better action. By measuring body weight and biochemical markers such as the level of serum creatinine and blood urea nitrogen, nephrotoxicity can be assessed. In the first stages of kidney disease, serum creatinine levels are the most potent indicator[27] .

In this study there were higher serum creatinine levels in treatment groups compared to control group, with significant increase of creatinine by increased dose of adenosine in treatment group. Creatinine is a result of chemical waste generated by muscle from the breakdown of a creatinine compound. Creatinine is absorbed by the kidneys from the body, filtering almost ever thing form the blood and releasing it into the urine. [28] . Increased plasma creatinine is almost always due to decreased GER and thus has a renal origin. While decreased GER (i.e. renal disease) is often associated with increased concentrations of plasma urea, there are other non-renal conditions that may lead to increased plasma urea. [19].

ALP is a group of iso enzymes that calalyze the hydrolysis of organic phosphate esters in the extracellular space located in the outer layer of the cell membrane. The bulk of ALP is released from the liver and bone. [29] [30]. In our current analysis, there is no significant differences between treatment and control groups in serum levels of alkaline phosphatase. This can be explained by the fact that ALP half- life in the circulation is around 1 week only, so it ALP levels typically increase and then slowly decrease thoughout the study period [31]. We also found that the serum levels of ALP were significantly lower in treatment groups that received higher doses of both adenosine and dipyridamole.this is in agreement with others. Shyamal et al., (In 2010)[39] showed the potential of antioxidant supplementation to lower serum liver enzyme levels (AST, ALT, ALLP and GGT) has been attributed to its protective action against cell necrosis. As dipyridamole has antioxidant properties, it induces a substantial decrease in the activity of AST and ALP serum liver enzymes in rabbits. [33][34][35] Choi et al., (2010) have shown that the biological activity of natural antioxidants plays a major role in reducing the serum activity of different liver enzymes. The effects of dipyridamole on is chemic/ reperfusion injury have been studied in numerous studies.

[36]Vargas et al., (2003) reported in a review of the antioxidant properties of dipyridamole that dipyridamole acts as a lipid peroxidation in hibitor and scavenges reactive oxygen radicals (ROS) by human ploymorphonuclear leukocytes. Also in disagreement with our results, other studies stated that adenosine in a large quantities and for a long time, it is considered an inflammatory and an oxidizing agent as well, so adenosine has been found to cause hepatic oxidative damage, thereby increasing the efficacy of AST, ALT, ALP and bilirubin content of liver enzymes in the serum.[37] .

In various types of liver cells, ROS, including superoxide anion radicals ($O\ 2^{-}$) and hydrogen peroxide (H_2O_2) are continuously developed in tracellularly as energy metabolism products [38]. Hepatic lipid overload causes oxidant overproduction by influencing multiple pathways that produce ROS. ROS induces oxidative changes to cellular macromolecules (DNA, lipids, proteins, etc) at high concentrations and contributes to the accumulation of damaged macromolecules, causing liver injury [39]. Elevated liver enzymes also mean that the cells in the liver are inflamed or damaged. Inflamed or damaged liver cells leak into the bloodstream more than average quantities of such substances, including liver enzymes, such as enzymes (ALT, AST, AL and GGT) [40] .

Lactate dehydrogenase is a widely distributed enzyme in different living cells. The heart, liver, skeletal muscle, kidney, and erythrocytes are found with high LDH activity [41]. The findings of the current study showed that the amount of LDH in the blood serum of rabbits in the adenosine and dipyridamole groups increased significantly after 30 days of the study relative to the control group. Increases in enzymes are generally linked to their leakage from damaged cells. In humans, the activity and release of inflammatory mediators and cell damage markers such as lactate dehydrogenase to average body [42]. Liver diseases, such as infectious hepatitis, acute myocardial infarction, skeletal muscle diseases and certain leukaemia, such as lymphoblastic leukaemia, also lead to elevated levels of LDH [43,41] .

As a result of organ destruction, elevated serum LDH occurs due to substantial cell death that results in cytoplasm loss. Tissue damage can be caused by diseases such as acute myocardial infarction, anemia, hepatitis, acute renal failure, pulmonary embolism, ect [44]. The rise in serum LDH may be due to mitochondrial function failure. This shows that with a decrease in the activity of the krebs cycle enzyme, an increase in LDH concentration, at the same time, it suggests a change from aerobic ti anaerobic status in energy output [45].

The findings of the current study showed an increase in the concentration of AST and LAT enzymes in the serum of rabbits in the adenosine and dipyridamole groups relative to the control group after 30 days of the experiment. Liver enzymes are liver- generated compounds that can be tested using a blood test. Any elevation in the level of an enzyme can be a symptom of a liver issue, and two of the enzymes essential to such an investigation are aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In contrast, AST and ALT can help detect liver toxicity, liver failure or liver damage [46]. In the liver, Kidney, brain, lung and skeletal muscle, (AST) is typically found, whereas (ALT) is predominantly present in the hepatocyte cytoplasm. Abnormal conditions indicate liver cell damage. Elevated ALT is more reflective of liver damage than AST since additional hepatic disease causes AST elevation as well. [47].

Increased serum levels of the ALT and AST enzymes are due to disruption to the hepatic cell membrane and the release of hepatocyte enzymes into the bloodstream. The findings of our current research are consistent with prior studies [48,49]. The increase in the concentrations of these enzymes was linked to hepatocyte damage and liver dysfunction, as they

noted. There is also an increase in liver tissue concentrations of ALT and AST. In general, liver enzyme induction is an adaptive response associated with increased liver weight, gene expression induction, and hepatocyte morphological changes.When liver responses surpass adaptive changes or decreased enzymes produce toxic metabolites, toxicity and heap to carcinogenicity can occur. It was reported that serum elevation of these enzymes (AST and ALT) was mainly due to acute hepatocellular damage or extra hepatic obstruction, or both. During hepatocellular injury, these enzymes were secreted into the blood and their levels increased [50].

However, in our current study, it was observed that was a decrease in the concentration of the enzyme GPT in the serum of rabbits in the adenosine group compared with the dipyridamole and control groups. The decrease in the concentration of the enzyme ALT may be due to the fact that therapeutic doses of adenosine had short half- life and toxic effects of adenosine on serum enzymes are kept to a minimum. [51]. Several authors have previously identified of that adenosine offers greater protection against injury to tissues. An increase in antioxidant potential, in particular by stimulating the activites of glutathione peroxidase (GPX-1) and catalase (CAT), has been associated with this protective impact. GPX-1 is an enzyme containing selenium that plays an important role in the defense of antioxidants by degrading H_2O_2 and lipid hydroperoxide. So the adenosine exerting antioxidant effects. This resulted in a decrease in the concentration of ALT enzyme in the adenosine group [52].

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تأثير الادينوسين والديبيريدامول على مستويات بعض المؤشرات الكيموحياتية في الارانب

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الملخص

الادينوسين هو نيوكليوسيد يحدث بشكل طبيعي وباشكال مختلفة من جميع خلايا الجسم وفي معظم السوائل البايولوجية وفي ظل الظروف الطبيعية تم الحفاظ على تركيز الادينوسين خارج الخلية ضمن حدود ميعنة يمنع الديبيريدامول امتصاص الادينوسين بواسطة كريات الدم الحمراء والخلايا البطانية والصفائح الدموية مما يزيد من مستويات الادينوسين في البلازما . الهدف : دراسة تأثيرات الادينوسين والديبيريدامول على مستويات مصل الدم من اليوريا، ألكرياتنين، الفوسفاتيز القلوي (ALP)، اللاكبيت ديهايدروجينيز (LDH) ، انزيم ناقله امين الغلوماتيك للبيروفيك (GPT) وانزيم ناقة امين الفلوتاميل للاكسالواستيتك (GOT) . المواد وطرائق العمل : تضمنت الدراسة الحالية 35 من ذكور الارانب قسمت الحيوانات الى 3 مجموعات :

المجموعة الاولى (5 حيوانات) : حقنت (i.p) بـ 2 مل من الماء المقطر / يوم (مجموعة السيطرة) .المجموعة الثانية (15 حيوان) عولجت بالحقن داخل الصفاق بمادة الادينوسين وقسمت الى 3 مجموعات فرعية (5 حيوانات) حسب جرعة الاديونسين: 1 ملغم / كغم . 2 ملغم / كغم و 4 ملغم/ كغم .

المجموعة الثالثة (15 حيوان): عولجت بالديبيريدامول عن طريق الغم / وقسمت الى 4 مجموعات فرعية 5 حيوانات) حسب جرعة الديبريدامول: 4 ملغم / كغم، 8 ملغم / كغم و 12 ملغم / كغم. النتيجة: تم العثور على فروق ذات دلالة إحصائية بين 3 مجموعات في مستويات اليوريا في الدم، LDH ، GOT ، ومستويات GPT. بينما أظهر التحليل الإحصائي لمستويات المصل من S. الكرياتينين و ALP عدم وجود فروق ذات دلالة إحصائية بين مجموعات الدراسة 3. الخلاصة: تسبب كل من الأدينوزين والديبيريدامول اختلافات كبيرة بين 3 مجموعات في اليوريا في الدم ومستويات LDH و GOT ومستويات GPT في الأرانب.