ORIGINAL ARTICLE

Comparison of the Hypertransferasemic Effects of Erythropoietin and U-74389G on Aspartate Aminotransferase Levels

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ABSTRACT

Aim: This study calculated the effects on aspartate aminotransferase (AST) levels, after treatment with either of two drugs: The erythropoietin (Epo) and the antioxidant lazaroid (L) drug U-74389G. The calculation was based on the results of two preliminary studies, each one of which estimated the certain influence, after the respective drug usage in an induced ischemia-reperfusion (IR) animal experiment. **Materials and Methods:** The two main experimental endpoints at which the serum AST levels were evaluated were the 60th reperfusion min (for the Groups A, C, and E) and the 120th reperfusion min (for the Groups B, D, and F). Especially, Groups A and B were processed without drugs, Groups C and D after Epo administration, whereas Groups E and F after the L administration. **Results:** The first preliminary study of Epo presented a significant hypertransferasemic effect by 19.73 ± 7.71% (P = 0.0119). The second preliminary study of U-74389G presented a non-significant hypertransferasemic effect by 16.23 ± 8.59% (P = 0.0583). These two studies were coevaluated since they came from the same experimental setting. The outcome of the coevaluation was that L is 0.8224656-fold (0.8211631–0.8237701) less hypertransferasemic than Epo (P = 0.0000). **Conclusions:** The antioxidant capacities of U-74389G ascribe 0.8224656-fold less hypertransferasemic effects than Epo (P = 0.0000).

Key words: Aspartate aminotransferase levels, erythropoietin, ischemia, reperfusion, U-74389G

INTRODUCTION

The lazaroid U-74389G (L) may be not famous for its hypertransferasemic[1] capacity (P = 0.0583). U-74389G as a novel antioxidant factor implicates exactly only 260 published studies. The ischemia-reperfusion (IR) type of experiments was noted in 18.84% of these studies. A tissue protective feature of U-74389G was obvious in these IR studies. The U-74389G chemically known as 21-[4-(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-pregna-1,4,9(11)-triene-3,20-dione maleate salt is an antioxidant complex, which prevents the lipid peroxidation either iron-dependent or arachidonic acid-induced one. Animals' kidney, liver, brain microvascular

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endothelial cell monolayers, and heart models were protected by U-74389G after IR injury. U-74389G also attenuates the leukocytes, downregulates the pro-inflammatory gene, treats the endotoxin shock, produces cytokine, enhances the mononuclear immunity, protects the endothelium, and presents anti-shock property.

Erythropoietin (Epo) even if is not famous for its hypertransferasemic action (P = 0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 30,606 published biomedical studies, only a 3.57% of them negotiate the known type of IR experiments. Nevertheless, Epo as a cytokine, it is worth of being studied about its effects on aspartate aminotransferase levels (AST) levels too.

This experimental work tried to compare the effects of the above drugs on a rat-induced IR protocol. They were tested by calculating the serum AST level (sASTl) augmentations.

MATERIALS AND METHODS

Animal preparation

The Vet licenses under 3693/12-11- 2010 and 14/10-1-2012 numbers, the granting company, and the experiment location are mentioned in preliminary references.[1,2] The human animal care of albino female Wistar rats, 7 days' pre-experimental *ad libitum* diet, non-stop intraexperimental anesthesiologic techniques, acidometry, electrocardiogram, oxygen supply, and post-experimental euthanasia are also described in preliminary references. Rats were 16–18 weeks old. They were randomly assigned to six (6) groups consisted of n = 10. The stage of 45 min hypoxia was common for all six groups. Afterward, reperfusion of 60 min was followed in Group A; reperfusion of 120 min in Group B; immediate Epo intravenous (IV) administration and reperfusion of 60 min in Group C; immediate Epo IV administration and reperfusion of 120 min in Group D; immediate U-74389G IV administration and reperfusion of 60 min in Group E; and immediate U-74389G IV administration and reperfusion of 120 min in Group F. The dose height assessment for both drugs is described at preliminary studies as 10 mg/kg body mass.

Ischemia was caused by laparotomic clamping the inferior aorta over renal arteries with forceps for 45 min. The clamp removal was restoring the inferior aorta patency and reperfusion. After exclusion of the blood flow, the protocol of IR was applied, as described above for each experimental group. The drugs were administered at the time of reperfusion, through inferior vena cava catheter. The ASTl was determined at 60th min of reperfusion (for A, C, and E) and 120th min of reperfusion (for Groups B, D and F). Along, a weak relation was rised between ASTl values with animals' mass (P = 0.2154), so it was no use of calculating the predicted ASTl values for the animals' mass.

Statistical analysis

Table 1 presents the (%) hypertransferasemic influence of Epo regarding reoxygenation time. Furthermore, Table 2 presents the (%) hypertransferasemic influence of U-74389G regarding reperfusion time. Chi-square tests were applied using the ratios which produced the (%) results per endpoint. The outcomes of Chi-square tests are depicted in Table 3. The statistical analysis was performed by Stata 6.0 software (Stata 6.0, StataCorp LP, Texas, USA).

Table 1: The % hypertransferasemic influence of erythropoietin in connection with reperfusion time

Hypertransferasemia value (%)	±SD (%)	Reperfusion time	*P* value
+29.53	±31.07	1 h	0.0096
+26.71	±36.79	1.5 h	0.0235
+23.89	±39.90	2 h	0.1709
+27.58	±47.72	Reperfusion	0.0271
+19.73	±7.71	Interaction	0.0119

SD: Standard deviation

Table 2: The % hypertransferasemic influence of U-74389G in connection with reperfusion time

Hypertransferasemia (%)	±SD (%)	Reperfusion time	*P* value
+33.94	±44.36	1 h	0.0328
+24.97	±50.25	1.5 h	0.0593
+16%	±51.91	2 h	0.4077
+21.05	±64.76	Reperfusion	0.1524
+16.23	±8.59	Interaction	0.0583

SD: Standard deviation

Table 3: The U-74389G/erythropoietin efficacy ratios on serum aspartate aminotransferase levels after Chi-square test application

Odds ratio	(95% Conf. interval)	*P* values	Endpoint
1.149264	1.006956 1.311683	0.0391	1 h
0.9347365	0.9334662 0.9360085	0.0000	1.5 h
0.6695775	0.5800545 0.7729184	0.0000	2 h
0.7631082	0.7620376 0.7641804	0.0000	Reperfusion
0.8224656	0.8211631 0.8237701	0.0000	Interaction

RESULTS

The successive application of Chi-square tests revealed that U-74389G augmented the ASTl by 1.149264-fold (1.006956–1.311683) more than Epo at 1 h (P = 0.0391), by 0.9347365-fold (0.9334662–0.9360085) less than Epo at 1.5 h (P = 0.0000), by 0.6695775-fold (0.5800545–0.7729184) less than Epo at 2 h (P = 0.0000), less by 0.7631082 (0.7620376–0.7641804) (P = 0.0000) without drugs, and by 0.8224656-fold (0.8211631–0.8237701) less than Epo whether all variables have been considered (P = 0.0000).

DISCUSSION

The unique available study investigating the hypertransferasemic effect of U-74389G on ASTl was the preliminary one.[1] Apart from the most famous activities this drug has as the neuroprotection and membrane-stabilization properties, it also accumulates in the cell membrane, protects the vascular endothelium from peroxidative damage, but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchenne muscular dystrophy. It increases γgt, superoxide dismutase, and glutathione levels in oxygen-exposed cells. It treats septic states and acts as immunosuppressant in flap survival. It prevents the learning impairments; it delays the early synaptic transmission decay during hypoxia improving energetic state of neurons. It shows antiproliferative properties on brain cancer cells and is considered as a new promising anti-inflammatory drug for the treatment of reperfusion syndrome in IR injuries.

The same authors confirmed[2] the short-term hypertransferasemic effect of Epo preparations in non-iron-deficient individuals. Li *et al*. demonstrated[3] that EPO may play a protective role against LPS-induced multiple organ failure by reducing the inflammatory response and tissue degeneration, possibly through the phosphatidylinositol 3-kinase/AKT and NF-κB signaling pathways restoring the LPS-induced ASTl in rats. Fu *et al*. examined[4] the protective effect of rHuEPO which is mediated through the activation of the phosphatidylinositol-3 kinase/AKT/endothelial nitric oxide synthase (eNOS) signaling pathway, at least in part, by increasing p-AKT and p-eNOS, and leads to the maintenance of an elevated level of NO in I/R injury of the liver. Yildar *et al*. investigated[5] the protective effect of 2-aminoethyl diphenylborinate which significantly reduced the sAST in the rat kidney I/R injury group. Bayramoglu *et al*. examined[6] the use of lycopene, while improvements of the AST values were partial and dose-dependent ($P < 0.05$) in IR injury of rat liver. Liu *et al*. showed[7] that quercetin significantly reduced apoptosis rate, improved cardiac function, and decreased the levels of AST, by inhibiting apoptosis *in vivo* and PI3K/AKT pathway involved in the anti-apoptotic effect in SD rats in myocardial IR injuries *in vivo*. Bayramoglu *et al*. noticed[8] that gallic acid significantly decreased the AST activities in tissue homogenates than no treatment group ($P < 0.05$) in oxidative stress generated by hepatic I/R-induced control rats. Matsuno *et al*. found[9] the ASTl in the control versus hydrogen group in 30, 60, and 120 min after reperfusion being more by 8.9%, 9.59%, and 3.54%, respectively, in a porcine liver reperfusion injury. Saïdi *et al*. compared[10] the control group with animals treated with tilapia fish oil which experienced a significant decrease ($P < 0.05$) in ASTl in reperfusion periods in male Wistar rats subjected to warm liver IRI. Li *et al*. significantly ameliorated[11] the I/R injury of the liver after Mino treatment, as shown by decreased Suzuki scores and liver function AST in male Sprague-Dawley rats liver. Ozkan *et al*. concluded[12] that hypothermic reperfusion and O_3 preconditioning might be beneficial in skeletal muscle IR injury since the ASTl were decreased than those in the IR group in the rats. Hu *et al*. found[13] the AST activities declined ($P < 0.05$) in tanshinone IIA (TSA) L-TSA, M-TSA, and H-TSA rat myocardial ischemia groups. Cahova *et al*. indicated[14] that metformin treatment prevented an acute stress-induced necroinflammatory reaction, reduced AST serum activity, diminished lipoperoxidation, and reduced mitochondrial performance but concomitantly protected the liver from I/R-induced injury in Wistar rats. Yildiz *et al*. showed[15] a decrease in ASTl in the micronized purified flavonoid fraction-treated rats than hepatic I/R group rats ($P < 0.001$ for all). Zhang *et al*. indicated[16] that hydrogen inhalation at 2% concentration for 1 h before liver syngeneic orthotopic transplantation protected from ischemia/reperfusion injury by activation of the NF-κB signaling pathway, reducing the sAST activities in rats. Lee *et al*. found[17] hepatocytes AlbCre+/constitutively active nuclear factor (erythroid-derived 2)-like 2 (caNrf2)+ having significantly reduced serum transaminases than wild-type littermate controls in warm hepatic murine IRI. Tang *et al*. regarded[18] Dioscorea nipponica Makino, D. panthaica Prain et Burkill (DP), and D. zingiberensis C.H. Wright (DZ) as having the same traditional therapeutic actions, such as TS

Table 4: A U-74389G/erythropoietin efficacy ratio meta-analysis on 20 hematologic variables (16 variables with balancing efficacies and 4 variables with opposite efficacies)[39,40]

Variable	Endpoint									
	1 h	*P* value	1.5 h	*P* value	2 h	*P* value	Reperfusion time	*P* value	Interaction	*P* value
Variable										
WBC	0.957451	0.3782	1.396122	0.0000	1.918237	0.0000	1.71622	0.0000	1.601887	0.0000
RBC count	0.961059	0.0000	1.733395	0.0000	6.519657	0.0000	1.039524	0.0000	1.309673	0.0000
Hematocrit	38.424	0.0000	9.076658	0.0000	6.222898	0.0000	1.001356	0.2184	12.66419	0.0000
Hemoglobin	1.268689	0.0000	1.839035	0.0000	13.1658	0.0000	1.252422	0.0000	1.94889	0.0000
MCH	151.125	0.0000	4.246814	0.0000	2.709729	0.0000	1.177347	0.0000	4.362893	0.0000
MCV	150.8518	0.0000	4.236722	0.0000	2.704247	0.0000	1.180156	0.0000	4.352528	0.0000
RbcDW	3.306773	0.0000	3.023389	0.0000	2.655885	0.0000	0.2259914	0.0000	2.370353	0.0000
Platelet count	2.42839	0.0000	6.00238	0.0000	6.1333429	0.0000	3.939027	0.0000	37.62979	0.0000
MPV	145.8532	0.0000	4.053619	0.0000	2.603947	0.0000	1.2334644	0.0000	4.164431	0.0000
Platelet DW	0.6940233	0.0000	1.319118	0.0000	2.206972	0.0000	2.2484006	0.0000	2.458888	0.0000
Glucose	156.4991	0.0000	4.53659	0.0000	2.81397	0.0000	0.9073196	0.0000	4.660603	0.0000
Urea	158.4209	0.0000	4.50889	0.0000	2.850291	0.0000	0.9017775	0.0000	4.632148	0.0000
Creatinine	168.9034	0.0000	4.872332	0.0000	3.039572	0.0000	1.0262016	0.0000	5.005523	0.0000
Total proteins	155.9562	0.0000	4.421079	0.0000	2.803573	0.0000	0.8842162	0.0000	4.541934	0.0000
Albumins	0.2457507	0.0073	0.5303472	0.0000	0.6243052	0.0465	1.237477	0.0000	0.5000416	0.0000
ALP	134.0033	0.0000	3.602703	0.0000	2.349961	0.0000	0.7205412	0.0000	3.701187	0.0000
Mean	15.968668	0.0239	3.060916	0.0000	3.093882	0.0028	1.10692926	0.0135	3.6055662	0.0000
Mean corpuscular hemoglobin concentrations	−0.2774225	0.0000	−0.5504722	0.0000	−8522433	0.0000	+3.044774	0.0000	−0.7793243	0.0000
Platelet crit.	−0.2312044	0.0000	−0.6719365	0.0000	−1.330756	0.0886	+5.620077	0.0000	−0.9771515	0.0000
ALT	+0.5955473	0.0000	−1.157335	0.0000	+7.967324	0.0000	+0.4734427	0.0000	−0.6208232	0.0000
γGT	1	1.0000	+0.5367033	0.0000	−0.9428571	0.8982	+2.146813	0.0000	−0.2683513	0.0000
Mean	−0.4757810	0.0250	−0.9450332	0.0000	−0.6052695	0.2467	+2.0421598	0.0000	−0.5968125	0.0000

groups exhibiting significantly reduced activities of AST than the model group (ISO injection only). Yucel *et al*. noticed that infliximab significantly reduced[19] the ASTl in IR liver. Deng *et al*. significantly reduced the levels of AST[20] in the MT group at each time point than that of the liver function IR group ($P < 0.05$) in male Sprague-Dawley rats. Lee *et al*. acknowledged that[21] treatment with eupatilin significantly decreased sAST as well as liver histologic changes in acute IR-induced hepatic damage. Ozsoy *et al*. found remarkably higher sASTl[22] in IR group than the sham group and the laboratory tests returned to normal levels in IR+melatonin (MEL) group after MEL treatment of the hepatic tissue. Bektas *et al*. found sAST[23] significantly different in tadalafil and pentoxifylline groups than liver IR group. Younis *et al*. investigated[24] the Silymarin preconditioning which decreased AST and improved hepatic architecture in HIR injury of insulin-resistant rats. Abdelsameea *et al*. pretreated with liraglutide which decreased[25] AST activities with attenuation of necrosis and inflammation while enhanced Bcl-2 expression in liver IR male rats. Liu *et al*. shown[26] that the formula of Guanxin Dhutong capsule which has four main active ingredients, protocatechuic acid, cryptotanshinone, borneol, and eugenol, diminished the infarct size and reduced ASTl *in vivo* in a rat model of the coronary artery. Hao *et al*. noticed that propofol significantly reduced[27] the activities of sAST in QSG-7701 cells *in vitro* of hepatic I/R injury in rats. Wang *et al*. revealed[28] that 2'-O-galloylhyperin effectively ameliorated CCl_4-induced hepatic damage by reducing AST activities in an animal model. Saidi *et al*. invented that *Pistacia lentiscus* oil decreased[29] both the visible severe intestinal damage and the sASTl in intestinal IR. Cai *et al*. pretreated with salidroside (20 mg/kg/day for 7 days, intraperitoneally) which significantly decreased[30] sAST levels after 6 h and 24 h of reperfusion and protected the segmental (70%) warm hepatic liver against I/R-induced injury. Wang *et al.* found[31] that flavonol glycosides which are in high concentrations in *Inula racemosa* altered cellular morphology, and cytokines and AST were returned to near normal level in hepatic I/R injury. Ardasheva *et al*. elevated the intra-abdominal pressure (IAP) above 20 mmHg which led[32] to progression of abdominal compartment syndrome that is associated with organ dysfunction or failure and elevated activities of AST found in some of the experimental groups than control ones of animals not subjected to increased IAP and time frame tested for liver. Zazueta *et al*. found[33] that citicoline CDP-choline reduced ASTl in blood samples from reperfused rats in I/R rat livers. Miyauchi *et al*. evaluated the levels of sAST as well as the scores of liver necrosis[34] significantly lower in the antioxidative nutrient-rich enteral diet (Ao diet) group than the control diet group in liver IR mice. Zhang *et al*. showed that[35] the role of hydrogen-rich saline treatment significantly decreased serum levels of AST activity and TUNEL-positive cells in miniature pig model of laparoscopic HIRI on hepatectomy. Chen *et al*. observed[36] significantly decreased (all $P < 0.05$) the levels of AST in the rosiglitazone group than the HIRI group in a rat model of hepatic ischemia-reperfusion injury. Gholampour *et al.* treated[37] with remote ischemic perconditioning and quercetin which reduced plasma AST activity in the liver after renal I/R. Brandão *et al*. observed[38] separately the protective effects of allopurinol and the benefits of ischemic post-conditioning by measuring ASTl with significantly reduced I/R systemic injuries in rats.

According to above, Table 3 shows that U-74389G has 0.8224656-fold (0.8211631–0.8237701) less hypertransferasemic effect than Epo ($P = 0.0000$) whether all variables have been considered ($P = 0.0000$), a trend attenuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 20 other seric variables, provides comparable results [Table 4].[39,40]

CONCLUSION

The antioxidant agent U-74389G was proved having 0.8224656-fold (0.8211631–0.8237701) less hypertransferasemic effect than Epo whether all variables have been considered ($P = 0.0000$); a trend attenuated along the short-term time frame of the experiment in rats. A biochemical investigation remains about how U-74389G mediates in these actions.

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