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The Opposite Metabolic Effects of Erythropoietin and U-74389Gon Serum Alanine Amino Transferase Levels

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ABSTRACT

Aim:*This study calculated the metabolic capacities of 2 drugs: the erythropoietin (Epo) and the antioxidant lazaroid (L) drug U-74389G on serum alanine amino transferees (ALT) levels. The calculation was based on the results of 2 preliminary studies, each one of which estimated the influence on (ALTl) levels, after the respective drug usage in an induced ischemia reperfusion animal experiment.*

Materials and methods: The 2 main experimental endpoints at which the ALTl were evaluated was the 60th reperfusion min (for the groups A, C and E) and the 120th reperfusion min (for the groups B, D and F). Specially, the 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 non significant alanine hyper amino transfer asemic effect by 8.04%+11.37% (p=-value=0.4698). The second preliminary study of U-74389G presented a non significant alanine hypo amino transferasemic effect by 4.99%+6.79% (p-value=0.4527). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation of these 2 drugs, as easily can be perceived, is that have opposite effects on ALTL.*

Conclusion:*The anti-oxidant capacities of U-74389G ascribe opposite metabolic effects than Epo on ALTl.*

Keywords: *ischemia; erythropoietin; U-74389G; serum alanine amino transferees levels; reperfusion*

INTRODUCTION

The lazaroid U-74389G (L) is not famous for its alanine hypoaminotransferasemic1 capacity (p-value=0.4527). U-74389G as a novel antioxidant factor, implicates exactly only 258 published studies. The ischemia reperfusion (IR) type of experiments was noted in 18.60% 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 per oxidation either iron-dependent, or arachidonic acid-induced one. Animal kidney,

liver, brain micro vascular endothelial cells monolayers and heart models were protected by U-74389G after IR injury. U-74389G also attenuates the leukocytes; down-regulates the proinflammatory 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 alanine hyper amino transferasemic action2 (p-value=0.4698), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 30,404 published biomedical studies, only a 3.56% of them negotiate the known type of IR experiments. Nevertheless, Epo as a cytokine, it is worth of being studied about serum alanine amino transferees (ALT) levels too.

This experimental work tried to compare the effects of the above drugs on ALT levels (ALTl) in a rat induced IR protocol. They were tested by calculating the serum ALTl alterations.

Table1. *The (%) alanine hyperaminotransferasemic influence of erythropoietin in connection with reperfusion time*

Hyperamino transferasemia ± SD		Reperfusion time	p-value
+18.89%	±38.40%	1h	0.1372
+7.63%	±63.91%	1.5h	0.6396
-3.63%	±56.83%	2h	0.8617
+34.12%	±72.22%	reperfusion	0.0535
+8.04%	±11.37%	interaction	0.4698

Materials And Methods

Animal Preparation

The Vet licenses under 3693/12-11- 2010 & 14/10-1-2012 numbers, the granting company and the experiment location are mentioned in preliminary references1,2. The human animal care of Albino female Wistar rats, the 7 days pre-experimental ad libitum diet, the non-stop intra-experimental anesthesiologic techniques, the acidometry, the electrocardiogram, the 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 in N=10. The stage of 45 min hypoxia was common for all 6 groups. Afterwards, 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 are 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 ALTl levels were determined at 60th min of reperfusion (for A, C and E groups) and at 120th min of reperfusion (for B, D and F groups). However, the predicted ALTl values were not used since a weak relation was rised with animals' mass (p-value=0.1308).

Table2. *The (%) alanine hypaminotransferasemic influence of U-74389G in connection with reperfusion time*

Hypamino transferasemia±SD		Reperfusion time	p-value
+11.25%	±17.31%	1h	0.0686
-8.83%	±46.98%	1.5h	0.4168
-28.92%	±69.15%	2h	0.2206
16.15%	±44.80%	reperfusion	0.1309
-4.99%	±6.79%	interaction	0.4527

Statistical Analysis

Table 1 presents the (%) alanine hyper amino transferasemic influence of Epo regarding reperfusion time. Also, Table 2 presents the (%) alanine hypo amino transferasemic 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 at Table 3. The statistical analysis was performed by Stata 6.0 software [Stata 6.0, StataCorp LP, Texas, USA].

RESULTS

The successive application of chi-square tests revealed that U-74389G was less alanine hyper amino transferasemic by 0.5955473-fold [0.5308441 - 0.6681376] than Epo at 1h; opposite effects by 1.157335-fold [-1.155712 - -1.15896] at 1.5h, more alanine hypo amino transferasemic by 7.967324-fold [6.908933 - 9.187835] at 2h, less alanine hyper amino transferasemic by 0.4734427-fold [0.4730252 - 0.4738607] without drugs and opposite effects by 0.6208232-fold [-0.6198533 - -0.6217947] whether all variables have been considered (p-value=0.0000)

DISCUSSION

The unique available study investigating the alanine hypo amino transferasemic effect of U-74389G on ALTl was the preliminary one1. Although the most famous activities of neuro protection and membrane-stabilization properties, it accumulates in the cell membrane, protecting vascular endothelium from per oxidative damage but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchene muscular dystrophy. It increases gamma-glut amyl transferees (γgt), superoxide dismutase (SOD) and glutathione (GSH) 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 confirmed2 the short-term alanine hyper amino transferasemic effect of Epo preparations in non iron deficient individuals. Fu W et al stimulated3 the protective effect of rHuEPO mediated via the activation of the phosphatidylinositol-3 kinase/AKT/eNOS signaling pathway, at least in part, by increasing p- protein kinase B (PKB/AKT) AKT and p- endothelial nitric oxide synthase (eNOS) and leads to the maintenance of an elevated level of NO, whereas the serum levels of ALTlwere significantly decreased in liver I/R injury. Taïeb D et al identified4 a heterozygous missense mutation (c.1589C>T) in exon 12 of HIF2A, resulting in an alanine 530 substitution in the HIF-2α protein with valine (A530V) in a new case of bilateral pheochromocytoma (PHEO) and multiple paraganglioma (PGLs) associated with congenital polycythemia. Lin KR et al demonstrated5 that phosphorylation of GATA-1 at serine^{26} is also transiently induced in cells of the erythroid lineage (primary erythroblasts and erythrocyte-committed progenitors [EPs]) by Epo, the principal cytokine regulating erythropoiesis. Surprisingly, reduced CFU-E progenitor population in glutamic acid GATA-1(S26E) mice was mainly due to EPO-induced growth suppression of GATA-1(S26E) EPs. Carrión JA et al evaluated6 the efficiency of a multidisciplinary support programmer (MSP), to increase patient adherence and the efficacy of pegylated interferon alfa-2a and ribavirin important to achieve sustained virological response (SVR) in chronic hepatitis C (CHC). TaşlıF et al described7 the primary hyperoxaluria (PH) as a rare autosomal recessive disorder. Type 1 PH is the most common form and develops due to a defect in a liver specific enzyme the ALTl enzyme. Coilly A et al have significantly improved8 SVR rates in HCV G1 patients after liver transplantation after protease inhibitors as cyclosporine and tacrolimus with peg interferon /ribavirin. Ioannou GN et al negatively associated9 SVR independently with baseline serum aspartate amino transferase/ALTlratio ≥1.2; and positively associated with erythropoietin use during treatment [AOR 2.9 (1.6-5.0)] in HIV/HCV co-infected patients. Li XJ et al showed10 a modest effect in preventing lip polysaccharide (LPS)-induced elevation of ALTl after EPO treatment in (LPS)-induced multiple organ failure (MOF) by reducing the inflammatory response and tissue degeneration, possibly via the phosphatidylinositol 3-kinase/AKT and NF-κB signaling pathways in rats. Ribeiro IF et al investigated11 the influence of Epo(EPO T→G) and α-actinin-3 (ACTN3 R577X) polymorphisms on plasma ALTlin runners. Yang XF et al significantly decreased 12 the ALTl than the D-galactosamine (D-GalN)/lip polysaccharide (LPS)-induced model group pretreated with EPO in fulminant hepatic failure mice. Toyoda H et al described13 a male patient with Pacak-Zhuang syndrome of paraganglioma, somatostatinoma, and polycythemia which carries a newly discovered C1589A mutation resulted in substitution of alanine 530 in the HIF-2α protein with glutamic acid. Yang Q et al indicated14 that oxymetholone can increase ALTl(MD 54.50 U/L) and compared with

Epoalone, nandrolone deaconate plus erythropoietin may increase HCT (MD 2.54%). Rjiba-Touati K et al explored15 the protective effect of rhEPO against Mitomycin C (MMC)-induced heart, liver, and renal dysfunction. The results showed that MMC induced a significant increase in ALTlin serum of adult male Wistar rats. Khodosovskiĭ MN et al shown16 that rhEPO infusion in dose 1000 IU/kg leads to oxyhemoglobin dissociative curve shift left-wards, improves prooxidant-antioxidant balance and plasma ALTl activities at the end of re-perfusion period in HIR. de Souza Crespo IC et al determined17 limits of 37 mg/L for alanine in a biopharmaceutical formulation containing recombinant human erythropoietin. Saab S et al counted18 baseline mean ALTlin fibrosing cholestatic hepatitis (FCH) recipients - an uncommon but potentially fatal complication of recurrent hepatitis C (HCV) in liver transplant recipients – by 2.26-fold less than in non-FCH recipients . Veillon P et al investigated19 the impact of epoetin beta (EPO) on sustained virological response (SVR) in hepatitis C virus (HCV)-infected patients treated with pegylated interferon-ribavirin (RBV). Independent factors associated with SVR were aspartate amino transferase /ALTl (AST/ALT) ratio in the anemic population. Zhong W et al found that curcumin inhibited20 c-AMP-responsive element-binding protein (CREB)/Caspase expression and decreased oxidative stress-associated protein expression, mainly involving 2E1 isoform of cytochrome P450/nuclear factor E2-related factor 2/reactive oxygen species (CYP2E/Nrf2/ROS) signaling pathway, along with ALT lregulations in livers of lipopolysaccharides LPS-induced rats. Hedayati MH et al revealed21 strongly 15.6-fold plasma half-life extension for the silico models of EPO fused to 200 amino acids of proline, alanine, and serine (PAS)ylated EPO (83.16 ± 13.28 h) in comparison to epoetin α (8.5 ± 2.4 h) and darbepoetin α (25.3 ± 2.2h) in normocythemic mice. Wadhawan M et al reported22 a rapid suppression of HCV RNA with a normalization of liver function tests within 4 weeks of starting therapy with sofosbuvir and ribavirin (within 6 months after transplant) in 3 cases with fibrosing cholestatic hepatitis. Wu S et al invented that helix B surface peptide helix B surface peptide (HBSP) significantly decreased23ALTlafter carbon tetrachloride CCl4 injection compared with control group in liver tissues. Koriem KMM et al. found24 significant increases in serum Epoand ALTlin 4-tert-octylphenol (OP), an endocrine-disrupting chemical that causes harmful effects to human health in OP toxicity groups of male albino rats. Altraif IH et al assessed25 the efficacy of PegIFNalfa-2a in combination with an adjusted (ADJ) RBV dose versus a fixed standard (STD) dose of RBV in chronic HCV genotype (GT) 4-naive patients. However, baseline ALTlwere not significantly different in patients achieving SVR. Tan H et al showed26 the concentrations of brain-derived ALTlwithout significant differences between their preoperative and postoperative values in either HIG or CG ($P > 0.05$) in intermittent whole-body hypoxic preconditioning on patients with carotid artery stenosis. Suh SW et al found that preoperative EPO treatment has27 a protective effect and stimulates liver regeneration, leading to improved overall survival following major hepatectomy decreasing hepatic ALTlafter 48hours in a cirrhotic rat model. Altavilla D et al produced28 endotoxin shock by a single intravenous (i.v.) injection of 20 mg/kg of Salmonella Enteritidis lipo polysaccharide (LPS) which enhanced plasma concentration of ALTlin male rats; treated with U-74389G (7.5, 15 and 30 mg/kg i.v.) or vehicle (1 ml/kg i.v.) 5 min after endotoxin challenge. Fukuma K et al investigated29 whether lazaroid U-74389G could attenuate endotoxin-induced liver injury by suppressing proinflammatory gene up-regulation. U-74389G treatment protected against lipo polysaccharide-induced liver injury in vivo, as indicated by the decreased hepatic lipid peroxidation, the inducible nitric oxide synthase messenger RNA formation and hepatic enzyme release in the liver. Alhan E et al investigated30 the influence of U-74389G on acute necrotizing pancreatitis (ANP) induced by glycodeoxycholic acid which resulted in a significant increase in pancreatic necrosis and serum levels of ALTl in bronchoalveolar lavage fluid in rats.

Table3. *The U-74389G / erythropoietin efficacies ratios on serum alanine amino transferees after chi-square tests application*

Odds ratio	[95% Conf. Interval]	p-values	Endpoint
0.5955473	0.5308441 0.6681376	0.0000	1h
-1.157335	-1.155712 -1.15896	0.0000	1.5h
7.967324	6.908933 9.187835	0.0000	2h

0.4734427	0.4730252 0.4738607	0.0000	reperfusion
-0.6208232	-0.6198533 -0.6217947	0.0000	interaction

Table4. *A U-74389G / erythropoietin efficacies ratios meta-analysis on 16 hematologic variableς (14 variables with balancing efficacies and 2 variables with opposite efficacies)31.*

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
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
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
Mean	11.6846761	0.0274	2.9560513	0.0000	3.1857468	0.0033	1.1361912	0.0155	3.5507569	0.0000

Endpoint / Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
Mean corpuscular haemoglobin concentrations	-0.2774225	0.0000	-0.5504722	0.0000	-0.8522433	0.0000	+3.044774	0.0000	-0.7793243	0.0000
Plateletcrit	-0.2312044	0.0000	-0.6719365	0.0000	-1.330756	0.0886	5.620077	0.0000	-0.9771515	0.0000
Mean	-0.2532076	0.0000	-0.6081795	0.0000	-1.0649544	0.0443	4.1366488	0.0000	-0.8726499	0.0000

According to above, table 3 shows that the anti-oxidant capacities of U-74389G ascribe opposite metabolic effects than Epo on ALTl. A meta-analysis of these ratios from the same experiment, for 16 other seric variables, provides comparable results (table 4)31.

CONCLUSION

The anti-oxidant capacities of U-74389G ascribe opposite metabolic effects than Epo on ALTl. A biochemical investigation remains about how U-74389G is implicated in these reactions.

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