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Comparison of the Hyperphosphatasemic Effects of Erythropoietin and U-74389G on Alkaline Phosphatase Levels

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ABSTRACT

Aim: *This study calculated the effects on alkaline phosphatase (ALP) levels, after treatment with either of 2 drugs: the erythropoietin (Epo) and the antioxidant lazaroid (L) drug U-74389G. The calculation was based on the results of 2 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 2 main experimental endpoints at which the serum ALP levels (ALPl) 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 hyper phosphatasemic effect by 5.18%+6.90% (p-value=0.4430). The second preliminary study of U-74389G presented a significant hyper phosphatasemic effect by19.18%+5.18%(p-value=0.0005). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that L is 3.701187-fold [3.697391 - 3.704987] more hyper phosphatasemic than Epo(p-value=0.0000).
Conclusions: The anti-oxidant capacities of U-74389G ascribe 3.701187-fold more hyper phosphatasemic effects than Epo (p-value=0.0000).

Key words: *ischemia; erythropoietin; U-74389G; alkaline phosphatase levels; reperfusion*

INTRODUCTION

The lazaroid U-74389G (L) may be famous for its hyperphosphatasemic[1] capacity (p-value=0.0005). U-74389G as a novel antioxidant factor, implicates exactly only 259 published studies. The ischemia reperfusion (IR) type of experiments was noted in 18.53% 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. Animal kidney, liver, brain microvascular 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 antishock property.

Erythropoietin (Epo) even if is not famous for itshyperphosphatasemicaction (p-value=0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 30,526 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 its effects on alkaline phosphatase levels (ALP) 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 ALP levels (ALPl) augmentations.

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 references[1,2]. 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 ALPlwere 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 ALPl values were used since a very significant relation was rised with animals' mass (p-value=0.0000).

Table 1. *The (%) hyperphosphatasemic influence of erythropoietin in connection with reperfusion time*

hyperphosphatasemia	±SD	Reperfusion time	p-value
+0.18%	±44.68%	1h	0.9904
+9.56%	±41.65%	1.5h	0.3549
+18.95%	±32.82%	2h	0.1509
-9.56%	±44.82%	reperfusion	0.3721
+5.18%	±6.90%	interaction	0.4430

Table 2. *The (%) hyperphosphatasemic influence of U-74389G in connection with reperfusion time*

Hyperphosphatasemia	±SD	Reperfusion time	p-value
+24.40%	±37.12%	1h	0.0663
+34.47%	±33.04%	1.5h	0.0001
+44.54%	±33.04%	2h	0.0003
-6.89%	±31.34%	reperfusion	0.4103
+19.18%	±5.18%	interaction	0.0005

Statistical analysis

Table 1 presents the (%) hyper phosphatasemic influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) hyper phosphatasemic 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 augmented the ALPlby

134.0033-fold [133.8097 - 134.1973] more than Epo at 1h (p-value=0.0000), by 3.602703-fold [3.599895 - 3.605513] more than Epo at 1.5h (p-value=0.0000), by 2.349961-fold [2.345418 - 2.354513] more than Epo at 2h (p-value=0.0000), less by 0.7205412-fold [0.7198176 - 0.7212655] (p-value=0.0000) without drugs and by 3.701187-fold [3.697391 - 3.704987] more than Epo whether all variables have been considered (p-value=0.0000).

DISCUSSION

The unique available study investigating the hyper phosphatasemic effect of U-74389G on ALPl was the preliminary one[1]. Although the most famous activities of neuro protection and membrane-stabilization properties, it accumulates in the cell membrane, protecting 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 (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 anti proliferative 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 hyperphosphatasemic effect of Epo preparations in non iron deficient individuals.Balzan SM et alobserved an increase in DNA damage after reperfusion[3] in the control group than in the Pharm PC group ($P < 0.05$), suggesting an early protective effect of PharmPC (lower levels of C-reactive protein soon after ischemia). Li R et al found[4] a milder degree of IR-induced hepatic injury, reflected by significantly lower levels of alkaline phosphatase after porta hepatis clamping in situ liver cold ischemia ISLCI than orthotopic liver transplantation Wistar rats. Karamanos D et al noted increased[5] ALP levels 30 minutes post-reperfusion also in the AT-III group than placebo (p=0.001) in an experimental animal model of tourniquet-induced skeletal muscle IR injury. Du Z et al found the levels of alkaline phosphatase enzymes significantly higher in the warm ischemic group than the sham-operated animals ($P<0.05$), with return to normal levels after two weeksin rat liver transplantation of induced[6] biliary duct injury Sprague-Dawley rats. Saidi SA et alreported[7] that Hammadascoparia (Pomel) (Chenopodiaceae) significantly ($p < 0.05$) reduced liver injury, as evidenced by the decrease both in liver alkaline phosphatase (ALP) and tissue oxidative stress levels through modulating SOD, GSH-PX, and CAT activities. O'Neill S et al described AT13387 as a novel heat shock protein 90 (Hsp90) inhibitor with low toxicity. In vitro, human embryonic kidney cells were co-transfected to express TLR4 and a secreted alkaline phosphatase NF-κB reporter. Shahbazi N et al classified[9] liver laboratory tests alterations as either hepatocellular damage or cholestatic damage (elevation of alkaline phosphatase and total bilirubin) or mixed. Bonatsos V et al found alkaline phosphatase (ALP)[10] statistically significantly reduced in treated groups (ALP: p=0.027) than control groups. Administration of U-74389G in liver IR injury has potential in attenuating liver damage. AthanasopoulosP et al investigated[11] the mRNA expression of genes exerting their inflammatory and regenerative reaction. Statistically significant differences were noticed in serum values of ALP in a IR swine model. Møller LN et al counted[12] alkaline phosphatase significantly higher in theantibody against the CD163 macrophage cell surface receptor and high dose dexamethasone (anti-CD163-dex) groups than control ones reducing the number of apoptotic cells following IR injuryin rat liver. Ghasemi M et al found that NG-nitro-L-Arginine methyl ester (L-NAME) as an NO inhibitor reduced[13] the liver tissue level of malondialdehyde and increased alkaline phosphatase levels on liver function in RIR model. Yu Y et al significantly reduced the levels of serum ALP and the level of nitrite in the kidney of the IRI group after pretreatment with honokiolthan control group in male adult Wistar albino rats. Mikrou A et al showed[15] that sevoflurane preconditioning significantly improved liver-biochemical tests including ALP levels and limited inflammatory cell infiltration in BALF, mediated by mechanisms that include ICAM1 and complement C3 down regulation in male Wistar rats. Oweira H et alassociated early allograft dysfunction representing[16] a hepatic injury with pre-transplant liver ALP levels not significantly different in both groups. Rayar M et al calculated[17] improved postoperative alkaline phosphatase levels in patients of temporary portocaval shunt (TPCS) group. Lauz Medeiros SH et al show[18] the protective effect of N-acetylcysteine NAC in the small intestine

impact of I/R liver damage. Ogunleye O et al hypothesized[20] that the pregnancy hormone relaxin would reduce cytotrophoblast apoptosis and necrosis (aponecrosis) and hence, the export of placental debris into the maternal circulation. The cells expressed placental alkaline phosphatase, aromatase, and human leukocyte antigen G. Pretreatment with LY294002 or MK-2206 inhibited the phosphatidylinositol 3-kinase-Akt/protein kinase B cell survival pathway, significantly blunting the cytoprotective effect of relaxin. Akbari G et al showed[21] that crocin protected the liver against IR injury through increasing the activity of antioxidant enzymes, improving serum levels of liver enzymes in rats. Hartmann R et alshowed[22] a significant reduction in serum alkaline phosphatase (ALP) levels in the glutamine+ intestinal I/R group than the intestinal I/R group. Najafi H et al led[23] to a significant increase in plasma concentrations of creatinine, urea, ALT and ALP levels after Malva sylvestris L. extract administration on ischemia-reperfusion-induced kidney and remote organ injuries in the liver. Wang Z et alreturned[24] altered cellular morphology, cytokines and alkaline phosphatase (ALP) to near normal levels after the root inularacemosa administration against hepatic I/R in male Albino Wistar strain rats. Echeverri J et al found alkaline phosphatase levels[25] lower in the BQ123(endothelin1 antagonist) and verapamil (calcium channel antagonist) groups than epoprostenol group. Qu B et al found the serum alkaline phosphatase levels lower in rat orthotopic liver transplantation model with extremely short anhepatic phase[26] protecting recipients and graft. Bouboulis G et al observed[27] 24% reduction for alkaline phosphatase ($P = 0.022$) in Group treated with lazaroid than the untreated group in the small intestine of swine models. Malek M et al found that gastric distension (GD) preconditioning decreased[28] alkaline phosphatase levels than sham GD group ($P < 0.05$) through anti-inflammatory activity.

According to above, table 3 shows that U-74389G hashyperphosphatasemic effects by 3.701187-fold [3.697391 - 3.704987] more than Epo whether all variables have been considered (p-value=0.0000); a trend attenuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 18 other seric variables, provides comparable results (table 4)[29-30].

Table 3. *The U-74389G / erythropoietin efficacies ratios on serum alkaline phosphatase levels after chi-square tests application*

Odds ratio	[95% Conf. Interval]		p-values	Endpoint
134.0033	133.8097	134.1973	1h	0.0000
3.602703	3.599895	3.605513	1.5h	0.0000
2.349961	2.345418	2.354513	2h	0.0000
0.7205412	0.7198176	0.7212655	reperfusion	0.0000
3.701187	3.697391	3.704987	interaction	0.0000

Table 4. *A U-74389G / erythropoietin efficacies ratios meta-analysis on 18 hematologic variableç (15 variables with balancing efficacies and 3 variables with opposite efficacies)*[29-30].

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
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
Mean	13.8573100	0.0255	3.0278414	0.0000	3.1511336	0.0030	1.1390705	0.0144	3.5992801	0.0000

Endpoint / Variable	**1h**	**p-value**	**1.5h**	**p-value**	**2h**	**p-value**	**Reperfusion time**	**p-value**	**interaction**	**p-value**
Mean corpuscular hemoglobin 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
ALT	+0.5955473	0.0000	-1.157335	0.0000	+7.967324	0.0000	+0.4734427	0.0000	-0.6208232	0.0000
Mean	-0.4757810	0.0000	-0.7536578	0.0000	-0.5221354	0.0295	+2.0084217	0.0000	-0.7790213	0.0000

CONCLUSION

The anti-oxidant agent U-74389G was proved havinghyperphosphatasemic effects by 3.701187-fold [3.697391 - 3.704987] more than Epo whether all variables have been considered (p-value=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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