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Research Article

Comparison of the Hypamylasemic Effects of Erythropoietin and U-74389G

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Abstract

Aim: This study calculated the effects on serum Amylase (A) 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 A levels 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, the groups C and D after Epo administration; whereas the groups E and F after the L administration.

Results: The first preliminary study of Epo presented a non significant hypamylasemic effect by 0.86%+1.14% (p-value=0.4430). However, the second preliminary study of U-74389G presented a significant hypamylasemic effect by 3.92%+1.06% (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 just by 4.561391-fold [4.553287 - 4.569509] more hypamylasemic than Epo (p-value=0.0000).

Conclusions: The anti-oxidant capacities of U-74389G ascribe just 4.561391-fold [4.553287 - 4.569509] more hypamylasemic effects than Epo (p-value=0.0000). However, a separate study is required for insulin and diabetes.

Keywords: Ischemia; Erythropoietin; U-74389G; Serum Amylase Levels; Reperfusion

Introduction

The Lazaroid U-74389G (L) may be not famous for its hypamylasemic [1]. Capacity (p-value=0.0005). U-74389G as a novel antioxidant factor, implicates exactly only 263 published studies. The Ischemia Reperfusion (IR) type of experiments was noted in 19.01% 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 its hypamylasemic [2]. Action (p-value=0.4430), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 31,593 published biomedical studies, only a 3.7% of them negotiate the known type of IR experiments. Nevertheless, Epo as a cytokine, it is worth of being studied about its effects on serum amylase (A) 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 A levels alterations.

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

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Table 1: The (%) hypamylasemic influence of erythropoietin in connection with reperfusion time.

Hypamylasemia	+SD	Reperfusion time	p-value
0.03%	8.25%	1h	0.9904
1.58%	6.91%	1.5h	0.3549
3.14%	5.44%	2h	0.1509
-1.58%	7.44%	reperfusion	0.3721
0.86%	1.14%	interaction	0.443

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 A 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). Along, powerful relation was rised between A values with animals' mass (p-value=0.0167); so as to predicted amylase values for rats' weights were used.

Statistical analysis

Table 1 presents the (%) hypamylasemic influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) hypamylasemic 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.

Result

The successive application of chi-square tests revealed that U-74389G caused hypamylasemia just by 156.4494-fold [156.3218 - 156.5771] than Epo at 1h (p-value=0.0000), just by 4.440002-fold [4.438149 - 4.441855] than Epo at 1.5h (p-value=0.0000), just by 2.813682-fold [2.804824 - 2.822567] than Epo at 2h (p-value=0.0000), by 0.8879931-fold [0.8864504 - 0.8895384] less than Epo (p-value=0.0000) without drugs and just by 4.561391-fold [4.553287 - 4.569509] than Epo whether all variables have been considered (p-value=0.0000).

Discussion

The unique available study investigating the hypamylasemic effect of U-74389G was the preliminary one1. Although the most famous activities of neuroprotection 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)

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

Hypamylasemia	+SD	Reperfusion time	p-value
5.26%	8.00%	1h	0.0663
7.05%	6.76%	1.5h	0.0001
8.84%	5.07%	2h	0.0003
-1.41%	6.41%	reperfusion	0.4103
3.92%	1.06%	interaction	0.0005

Table 3: The U-74389G/erythropoietin phosphoremic efficacies after chi-square tests application.

Odds ratio	[95% Conf. Interval]	p-values	Endpoint
156.4494	156.3218 156.5771	0	1h
4.440002	4.438149 4.441855	0	1.5h
2.813682	2.804824 2.822567	0	2h
0.8879931	0.8864504 0.8895384	0	interaction
4.561391	4.553287 4.569509	0	reperfusion

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 ant 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 hypamylasemic effect of Epo preparations in non iron deficient individuals. Ambrosi N et al showed [3]. That α-Lipoic Acid (ALA) preconditioning is capable of reducing inflammatory markers while decreasing early kidney dysfunction and clinical posttransplant pancreatitis in the simultaneous kidney-pancreas transplant graft and biochemical markers of IRI. Serum lipase and amylase were lower in the DR group than in the control and recipient groups. Pieńkowska J et al assessed [4]. The risk of developing severe form of acute pancreatitis both on the basis of scores based on clinical status and laboratory tests having low predictive value on the first day of onset of symptoms. Baser H et al positively correlated [5]. Ischemia-Modified Albumin (IMA) levels (p = 0.001); whereas negatively correlated TAS levels with amylase and lipase levels (p = 0.035) in patients with mild acute pancreatitis. Abogresha NM et al suggested [6,7]. That bilateral renal ischemia for 45 min caused significant impairment of pancreatic function and structure as indicators of acute pancreatitis. While IR enhances oxidative stress and apoptosis, vitamin C appears to play a cytoprotective role. Khoroshinina LP experienced the activity of pancreatic alpha-amylase stress-Valas on average 13 times the original values, the activity of one membrane enzymes--gamma-amylase as increased by 4 times under conditions of chronic ischemia at the proximal small intestine mucosa in dogs. Chaari A Increased serum amylase and/or lipase levels are [8] common in patients with septic shock without investigation for acute pancreatitis. Osuka A et al consider [9]. The intestinal fatty acid binding protein (I-FABP) as [9] A known biomarker for diagnosing intestinal ischemia/damage. A high I-FABP level on admission was associated with the subsequent development of multiple organ dysfunction and with the deep burn area. Hoyme M et al reported [10]. The case of an acute pancreatitis might present with ECG changes and symptoms in a 82-year-old woman who was admitted with acute chest pain, nausea, and vomiting; whereas serum amylase and lipase levels were 5 times above the normal range. Warzecha Z et al observed induced pancreatic IR accompanied [11] with a reduction in the serum activity of lipase and amylase, concentration of interleukin-1β and plasma d-Dimer concentration; as well an intravascular activation of coagulation in acute pancreatitis related with the severity of this inflammation in male rats. Kawatani Y et al necessitated [12] covering the artery with a stent graft due to the proximity of the aneurysm to the celiac

Table 4: A U-74389G/erythropoietin efficacies ratios meta-analysis on 32 hematologic variables [1].

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	1.918237	0	1.71622	0	1.601887	0
RBC count	0.961059	0	1.733395	0	6.519657	0	1.039524	0	1.309673	0
Hematocrit	38.424	0	9.076658	0	6.222898	0	1.001356	0.2184	12.66419	0
Hemoglobin	1.268689	0	1.839035	0	13.1658	0	1.252422	0	1.94889	0
MCH	151.125	0	4.246814	0	2.709729	0	1.177347	0	4.362893	0
MCV	150.8518	0	4.236722	0	2.704247	0	1.180156	0	4.352528	0
MCHC	3.6046103	0	1.8166222	0	1.1733738	0	3.044774	0	1.2831629	0
RbcDW	3.306773	0	3.023389	0	2.655885	0	0.2259914	0	2.370353	0
Platelet count	2.42839	0	6.00238	0	6.1333429	0	3.939027	0	37.62979	0
MPV	145.8532	0	4.053619	0	2.603947	0	1.2334644	0	4.164431	0
Platelet DW	0.6940233	0	1.319118	0	2.206972	0	2.2484006	0	2.458888	0
Platelet crit	4.3251772	0	1.4882359	0	0.7514526	0.0886	5.620077	0	1.0233828	0
Glucose	156.4991	0	4.53659	0	2.81397	0	0.9073196	0	4.660603	0
Urea	158.4209	0	4.50889	0	2.850291	0	0.9017775	0	4.632148	0
Creatinine	168.9034	0	4.872332	0	3.039572	0	1.0262016	0	5.005523	0
Uric acid	0.6212533	0	1.106911	0	1.3349	0.0027	0.4421801	0	1.33234	0
Total proteins	155.9562	0	4.421079	0	2.803573	0	0.8842162	0	4.541934	0
Albumins	0.2457507	0.0073	0.5303472	0	0.6243052	0.0465	1.237477	0	0.5000416	0
ALT	0.5955473	0	0.8640541	0	7.967324	0	0.4734427	0	1.6107645	0
AST	1.149264	0.0391	0.9347365	0	0.6695775	0	0.7631082	0	0.8224656	0
γGT	1	1	0.5367033	0	1.0606061	0.8982	2.146813	0	3.7264586	0
ALP	134.0033	0	3.602703	0	2.349961	0	0.7205412	0	3.701187	0
ACP	2.774031	0	5.450674	0	7.86942	0	0.121724	0	8.011334	0
CPK	144.0769	0	3.987264	0	2.567192	0	0.7974539	0	4.09626	0
CK-MB	141.313	0	3.883186	0	2.509108	0	1.2876033	0	3.989339	0
LDH	142.9228	0	3.944068	0	2.543149	0	1.2677226	0	4.051881	0
Sodium	1.695709	0	0.8085706	0	3.008772	0.0455	1.631842	0	2.74914	0
Potassium	1.640618	0	0.968488	0	3.346145	0	2.414214	0	11.4937	0
Chloride	0.5544784	0.0007	0.8643683	0	1.07745	0.5428	1.358293	0	1.012762	0
Calcium	3.34E-06	0	0.2490068	0	0.1988753	0	2.063208	0	2.3623042	0
Phosphorus	0.861859	0.1111	0.409606	0	0.167592	0	5.120084	0	0.445513	0
Magnesium	1.331108	0	0.2605466	0	0.5961915	0	1.013227	0	1.823808	0
Mean	4.7836821	0.0478	1.8652864	0	2.0706402	0.0504	1.1912709	0.0065	2.264798	0

artery origin. Postoperatively, nausea and abdominal pain appeared, and the amylase level and white blood cell count were elevated in a 69-year-old man. Anderson PT et al acknowledged [13] no differences between the groups with respect to amylase, lipase, or glycosated hemoglobin (HbA1c) up to 4 years after Simultaneous Pancreas and Kidney (SPK) transplants using Donation after Cardiac Death (DCD) donor organs in Canada. Apart from a higher renal DGF rate, SPK transplants with DCD donor organs have comparable outcomes to standard transplants with Neurologic Determination of Death (NDD) donor organs. Güldoğan CE et al found [14] no correlation between Ischemia-Modified Albumin (IMA) levels with amylase levels (p=0.470), Ranson score (p=0.664) and disease severity (p=0.741); so as the Ranson score still indicates the disease severity more accurately. Sommer CM et al assessed as key characteristics of both biodegradable prototypes (L1 and L2; prototype groups) [15] as follows: microspheres are biodegradable by serum α-amylase, produced from chemically crosslinked potato starch to different extents, in a diameter range of ~300-800 µm, differing in size distribution and featuring a microsphere deformation of ~1% in pig kidneys. Ardasheva RG et al found [16] elevated activities of aspartate aminotransferase, pancreatic amylase, lipase, and higher concentrations of D-lactate, urea, and creatinine in some of the experimental groups compared with a control group of animals not subjected to increased Intra-Abdominal Pressure (IAP) in a rat model of abdominal compartment syndrome. El Agaty SM et al assessed [17] the remote pancreatic injury following renal Ischemia/Reperfusion

(I/R) which significantly increased serum amylase, fasting glucose and decreased serum insulin in I/R versus sham group. Chen TH et al found [18] increased serum amylase and LDH and impaired the pulmonary barrier dysfunction in the PIR group than the sham group. Khan SM et al used [19] new markers alongside with the classical markers (amylase) in the context of a scoring system might help in making a diagnosis of Acute Mesenteric Ischemia (AMI) in emergency settings. Parikh MP et al found [20] often elevated white blood cell counts, serum lactate, and serum amylase levels in patients with ischemic colitis. Nano R et al found emerging [21] differences among facilities in donor selection (age, cold ischemia time, intensive care unit length, amylase concentration), pancreas procurement, and release criteria for transplantation (glucose-stimulated insulin secretion tests, islet numbers, and purity), highlighting the presence of a heterogeneity in the islet cell product process and product release criteria. Tatar C et al investigated [22] the diagnostic value of nesfatin-1 in cases of intestinal IR as a biomarker in acute mesenteric ischemia. Effoe VS et al described chest pain associated [23] with transient electrocardiogram changes mimicking an acute myocardial infarction in acute pancreatitis. Clinicians may consider deferring immediate cardiac catheterization and attribute electrocardiogram changes to acute pancreatitis in patients presenting with angina pectoris and acute pancreatitis if confirmed by normal cardiac enzymes and elevated levels of lipase and amylase. Kumano T et al found the amylase level of the drainage fluid [24] abnormally high on postoperative day 3 and contrast-enhanced CT confirmed gastric remnant necrosis in high surgical risk cases.

According to above, Table 3 shows that U-74389G has just 4.561391-fold [4.553287 - 4.569509] more hypamylasemic effect 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 32 other seric variables, provides comparable results (Table 4) [25].

Conclusion

The anti-oxidant agent U-74389G was proved having just 4.561391-fold [4.553287 - 4.569509] more hypamylasemic effect 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. Although the production organ of A and insulin is the same; the pancreas, a separate study is required for insulin and diabetes.

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Ethical Approval

"All applicable international, national, and/or institutional guidelines for the care and use of animals were followed."

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