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Research Article

The alterations effects in phosphorus of erythropoietin and U-74389G

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Abstract

Aim: This study calculated the effects on serum phosphorus (P) 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 P 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 hyperphosphoremic effect by 2.46% + 2.02% (p - value = 0.2168). However, the second preliminary study of U-74389G presented a non significant hypophosphoremic effect by 1.09% + 2.01% (p - value = 0.5771). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that L is at least 0.4455128-fold [0.4445589 - 0.4464687] more hypophosphoremic than Epo (p - value = 0.0000).

Conclusion: The anti-oxidant capacities of U-74389G ascribe at least 0.4455128-fold [0.4445589 - 0.4464687] more effects than Epo (p - value = 0.0000).

Introduction

The lazaroid U-74389G (L) may be not famous for its hypophosphoremic[1] capacity (p - value = 0.5771). U-74389G as a novel antioxidant factor, implicates exactly only 262 published studies. The ischemia reperfusion (IR) type of experiments was noted in 19.08% 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 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 hyperphosphoremic[2] action (p - value = 0.2168), it can be used as a reference drug for comparison with U-74389G. Although Epo is met in over 31,502 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 phosphorus (*p*) 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 *p* levels alterations. Phosphorus is essential for life. Phosphates (compounds containing the phosphate ion, PO_4^{3-}) are a component of DNA, RNA, ATP, and phospholipids. Elemental phosphorus was first isolated from human urine and bone ash was an important early phosphate source. Bone marrow is composed of hematopoietic cells, marrow adipose tissue, and supportive stromal cells. Human marrow produces approximately 500 billion blood cells per day, which join the systemic circulation. All types of hematopoietic cells, including both myeloid and lymphoid lineages, are created in bone marrow. Hematopoietic cells are very rich in DNA, RNA, ATP, and phospholipids. Since erythropoietin stimulates red blood cell production (erythropoiesis) in the bone marrow; an assumption was set that the alterations Epo causes on phosphorus levels, may reflect related alterations on erythropoiesis. It is claimed that epo may have antioxidant properties; thus, this assumption for epo is compared with a similar one with the antioxidant drug L.

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 *p* 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, non relation was rised between *p* values with animals' mass (*p* - value = 0.5911).

Statistical analysis

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

Results

The successive application of chi-square tests revealed that U-74389G caused hypophosphoremia at least by 0.86185944-fold [0.71786427 - 1.0347395] than Epo at 1h (*p* - value = 0.1111), at least by 0.4096059-fold [0.4088905 - 0.4103226] than Epo at 1.5h (*p* - value = 0.0000), at least by 0.1675922-fold [0.1672522 - 0.167933] than Epo at 2h (*p* - value = 0.0000), by 5.120084-fold [5.102681 - 5.137547] less than Epo (*p* - value = 0.0000) without drugs and at least by 0.4455128-fold [0.4445589 - 0.4464687] than Epo whether all variables have been considered (*p* - value=0.0000).

Discussion

The unique available study investigating the hypophosphoremic effect of U-74389G was the preliminary one[1]. Although the most famous activities of neuroprotection and membrane-stabilization properties, it accumulates in the cell membrane, protecting vascular endothelium from

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

Hypophosphoremia	± SD	Reperfusion time	*p* - value
1.92%	± 15.22%	1h	0.6982
3.95%	± 12.97%	1.5h	0.21
5.98%	± 10.65%	2h	0.1541
-0.35%	± 11.45%	reperfusion	0.9041
2.46%	± 2.02%	interaction	0.2168

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

Hypophosphoremia	± SD	Reperfusion time	*p* - value
-2.23%	± 12.78%	1h	0.6308
-1.62%	± 11.56%	1.5h	0.5789
-1%	± 10.92%	2h	0.7957
-1.80%	± 13.05%	reperfusion	0.5627
-1.09%	± 2.01%	interaction	0.5771

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

Odds ratio	[95% Conf. Interval]		*p* - value	Endpoint
0.861859	0.717864	1.03474	0.1111	1h
0.409606	0.408891	0.410323	0.0000	1.5h
0.167592	0.167252	0.167933	0.0000	2h
5.120084	5.102681	5.137547	0.0000	reperfusion
0.445513	0.444559	0.446469	0.0000	interaction

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 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 hyperphosphoremic effect of Epo preparations in non iron deficient individuals. Ozelsancak, et al. [3] reported that hemodialysis (HD) patients with CSVD had lower sCr ($p < 0.0001$) and phosphorus ($p < 0.007$) levels than normal subjects. Takahashi, et al. demonstrated [4] an increase in the magnetization transfer ratio asymmetry (MTRasym), which reflects Cr concentration of ischemic hindlimbs, along with a decrease of PCr; whereas they developed phosphorus magnetic resonance spectroscopy (31 P MRS) obtained at 11.7T calculated in severe ischemic, mild ischemic and control hindlimbs of mouse skeletal muscle in C57BL/6 mice. Dubský, et al. showed [5] a significant increase of transcutaneous oxygen pressure ($TcPO_2$) among the rest (phosphocreatine, adenosine triphosphate and inorganic phosphate) and dynamic (mitochondrial capacity and phosphocreatine recovery time) ^{31}P-MRS parameters at baseline and 3 months after autologous cell therapy on the dorsum of the foot. Stephens, et al. demonstrated [6] that a single high dose of phosphate (2,000 mg) did not augment blood pressure in response to exercise or isolated muscle metaboreflex activation in young healthy men. Wang Y, et al. claim that penehyclidine hydrochloride (PHC) can effectively antagonize [7] the symptoms of central and peripheral poisoning caused by organophosphorus poisoning. Gruson, et al. claimed [8] that the increase of fibroblast growth factor 23 (FGF-23), a key hormone for the regulation of the phosphorus homeostasis, participates to cardiac hypertrophy and remodeling in heart failure. Hart, et al. repeated [9] the free-flow control conditions (FF) and reactive hyperemia (RH) trials under hyperoxic conditions (FF + 100% O_2 and RH + 100% O_2) in skeletal gastrocnemius muscle of patients with peripheral artery disease. Anselmo, et al. attenuated [10] IR-induced renal changes, with reduction of plasmatic phosphorus as well as reducing kidney expression of iNOS, nitrotyrosine and macrophage influx after pre-treatment with 75 mg of Brazil nuts. Tarui, et al. evaluated [11] the outcome and risk factors related [11] with increased creatinine phosphorus kinase in patients undergoing minimally invasive cardiac operation in mitral valve problem. Dattilo, et al. associated [12] hypovitaminosis D beyond calcium and phosphorus with the genesis of rheumatic, autoimmune, neoplastic and cardiovascular diseases in patients particularly with heart failure. Hirose, et al. found [13] greater LV mass index or serum calcium-phosphorus product in dialysis patients with positive myocardial ischemia despite an FFR > 0.76. Abdurrachim, et al. investigated [14] cardiac energetics non-invasively *in vivo* by ^{31}P magnetic resonance spectroscopy (MRS), by detecting ^{31}P-containing metabolites involved in energy supply and buffering and understanding of cardiac energy metabolism in heart failure and diabetes. El Sharkawy, et al. observed [15] statistically significant higher levels of serum miRNA 499 in all the studied patients with cardiovascular diseases and complications than the levels of miRNA 499 in healthy controls ($p < 0.0001$). High-flux membrane seems to be less efficient in miRNA 499 clearance in cardiac patients on hemodialysis. Andrulli S, et al. significantly related [16] an increased risk of lower limb ulcers with blood levels of phosphorus among other variables in dialysis patients. Yuan, et al. analyzed [17] the effects of surgical total removal of parathyroid gland (PTG) tissue in rats. Chatel, et al. used [18] magnetic resonance spectroscopy of phosphorus 31, phosphocreatine and inorganic phosphate concentrations throughout two standardized protocols of a spontaneous muscular vaso-occlusive crisis in rest - exercise - recovery at two different intensities in sickle cell disease (SCD) mice. Němcová A, et al. found enabled [19] phosphorus magnetic resonance spectroscopy (^{31}P MRS) to evaluate oxidative muscle impaired metabolism in patients with complicated diabetes. Thus, significantly higher Pi and pH (both $p < 0.01$) were noticed in patients with CLI than healthy control ones. Ezzati et al. assessed [20] the whole-brain (phosphorus-31 and regional proton MRS biomarkers) nucleotide triphosphate/exchangeable phosphate pool was similar ($p = 0.73$) over 48h in large White male piglets. Kamath, et al. recommend [21] to all patients with a history of previous thyroid operation, who come with vague symptoms like fatigue, muscle aches to undergo estimation of serum calcium, phosphorus and parathyroid hormone (PTH) screened for delayed hypoparathyroidism. Carlbom et al. consider [22] phosphomonoesters(PME)/Pi ratio as the most discriminatory variable at prolonged CIT. ^{31}P-MRS may provide quantitative parameters for evaluating graft viability *ex vivo* and is a promising tool for objective non-invasive assessment of the quality of human pancreas grafts prior to transplantation or islet isolation. Lowe, et al. positively correlated [23] anti-inflammatory cytokine IL-17E with serum 25(OH) vitamin D insufficiency present in the majority of term HIE neonates. Layec, et al. assessed muscle metabolism and peripheral hemodynamics in healthy, untrained, elderly individuals subjected [24] to dynamic plantar flexion exercise and other imaging examinations including phosphorus magnetic resonance spectroscopy (31P-MRS). Groenendaal, et al. were [25] led to the concept of secondary energy failure after phosphorus magnetic resonance spectroscopy (MRS) in infants with HIE. Li, et al. found the ratio of pSer16-PLB/PLB expression to decrease calcium overload obviously decreased [26] ($p < 0.05$); whereas the sarcoplasmic reticulum calcium transport ATPase SERCA 2a expression risen in the gastrodin

group in a dose-dependent manner ($p < 0.05$) along with MIRI and inflammation injury alleviation. Liu, et al. acquired [27] ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) to quantify changes in phosphate metabolites and muscle oxygenation in Goto-Kakizaki (GK) non-obese type 2 diabetes (T2D) rats and Wistar (control) rats. Inci, et al. did not associated the soluble Klotho (s-Klotho) levels [28] with phosphorus and PTH levels in diabetic nephropathy patients. Brown, et al. related [29] the progression of established chronic kidney disease CKD with dietary phosphorus intake, in cats. Broad, et al. acquired [30] successive whole-brain phosphorus-31 and regional proton MRS after hypoxia-ischemia in newborn male Large White piglets. Ezzati, et al. assessed [31] increased whole brain phosphorus-31 MRS ATP ($p = 0.039$) and immediate remote ischemic postconditioning (RIPostC) as a brain protective therapy for babies with NE with protection in white matter over the 48h after HI in large White female newborn piglets. Wilder, et al. confirmed [32] by intracellular 31-phosphorus (^{31}P) nuclear magnetic resonance (NMR) spectroscopy that insertion of an intraventricular balloon IVB inflation has profound antiarrhythmic effects, likely due to inflation-induced localized ischaemia in rat Langendorff heart preparation.

The quoted references show the important diagnostic value of p through the metabolic level, as the buffering role of reoxygenation and cytokines on p levels. According to above, table 3 shows that U-74389G has at least 0.4455128-fold [0.4445589 - 0.4464687] more hypophosphoremic than Epo whether all variables have been considered (p - value = 0.0000); a trend accentuated along time, in Epo non-deficient rats. A meta-analysis of these ratios from the same experiment, for 30 other seric variables, provides comparable results (Table 4) [33].

Conclusion

The anti-oxidant agent U-74389G was proved having at least 0.4455128-fold [0.4445589 - 0.4464687] more hypophosphoremic 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.

Acknowledgement

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Ethical approval

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

Table 4: A U-74389G/erythropoietin efficacies ratios meta-analysis on 30 hematologic variables [33].

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
MCHC	3.6046103	0.0000	1.8166222	0.0000	1.1733738	0.0000	3.044774	0.0000	1.2831629	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
Platelet crit	4.3251772	0.0000	1.4882359	0.0000	0.75145256	0.0886	5.620077	0.0000	1.0233828	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
ALT	0.5955473	0.0000	0.86405406	0.0000	7.967324	0.0000	0.4734427	0.0000	1.6107645	0.0000
AST	1.149264	0.0391	0.9347365	0.0000	0.6695775	0.0000	0.7631082	0.0000	0.8224656	0.0000
γGT	1	1.0000	0.5367033	0.0000	1.0606061	0.8982	2.146813	0.0000	3.7264586	0.0000
ALP	134.0033	0.0000	3.602703	0.0000	2.349961	0.0000	0.7205412	0.0000	3.701187	0.0000
ACP	2.774031	0.0000	5.450674	0.0000	7.86942	0.0000	0.121724	0.0000	8.011334	0.0000
CPK	144.0769	0.0000	3.987264	0.0000	2.567192	0.0000	0.7974539	0.0000	4.09626	0.0000
CK-MB	141.313	0.0000	3.883186	0.0000	2.509108	0.0000	1.2876033	0.0000	3.989339	0.0000
LDH	142.9228	0.0000	3.944068	0.0000	2.543149	0.0000	1.2677226	0.0000	4.051881	0.0000
Sodium	1.695709	0.0000	0.8085706	0.0000	3.008772	0.0455	1.631842	0.0000	2.74914	0.0000
Potassium	1.640618	0.0000	0.968488	0.0000	3.346145	0.0000	2.414214	0.0000	11.4937	0.0000
Chloride	0.5544784	0.0007	0.8643683	0.0000	1.07745	0.5428	1.358293	0.0000	1.012762	0.0000
Calcium	0.00000334	0.0000	0.2490068	0.0000	0.1988753	0.0000	2.063208	0.0000	2.3623042	0.0000
Magnesium	1.331108	0.0000	0.2605466	0.0000	0.5961915	0.0000	1.013227	0.0000	1.823808	0.0000
Mean	5.4215438	0.0473	1.9963925	0.0000	2.2848353	0.0537	1.1728669	0.0069	2.4335985	0.0000

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