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Comparison of the Widening Capacities of Erythropoietin and U-74389g Concerning Platelet Distribution Width Levels

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ABSTRACT

This study calculated the widening capacities of 2 drugs: the erythropoietin (Epo) and the antioxidant drug U-74389G. The calculation was based on the results of 2 preliminary studies, each one of which estimated the platelet distribution width (PDW) levels augmentation, after the respective drug usage in an induced hypoxia reoxygenation animal experiment.

Materials and methods: *The 2 main experimental endpoints at which the PDW levels (PDWl) were evaluated was the 60th reoxygenation min (for the groups A, C and E) and the 120th reoxygenation 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 U-74389G administration.*

Results: *The first preliminary study of Epo non significantly increased the PDWl by 0.39%±0.37% (p-value=0.2830). Also, the second preliminary study of U-74389G significantly increased the PDWl by 0.97%±0.49% (p-value=0.0396). These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that U-74389G has 2.458888-fold more widening potency than Epo (p-value=0.0000).*

Conclusions: *The anti-oxidant capacities of U-74389G enhance the acute widening properties; presenting 2.458888-fold wider on PDWl than epo (p-value=0.0000).*

Keywords: *hypoxia; erythropoietin; U-74389G; platelet distribution width levels; re-oxygenation.*

INTRODUCTION

U-74389G is not famous for its widening[1] capacity (p-value=0.0396). U-74389G as a novel antioxidant factor, implicates exactly only 255 published studies. The hypoxia reoxygenation (HR) type of experiments was noted in 4.31% of these studies. A tissue protective feature of U-74389G was obvious in these HR 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 micro vascular endothelial cells monolayer's and heart models were protected by U-74389G after HR injury. U-74389G also Attenuates the leukocytes; down-regulates the proinflammatory gene; treats the end toxin shock; produces cytokine; enhances the mononuclear immunity; protects the endothelium and presents antishock property.

Erythropoietin (Epo) even if is not famous for its widening action (p-value=0.2830), it can be used as a reference drug in order a widening capacity of U-74389G to become comprehensible. Although Epo is met in over 29,654 published biomedical studies, only a 10.48% of them negotiate the known type of HR experiments. Nevertheless, Epo as a cytokine, never goes out of the jurisdiction of the platelet distribution width study.

This experimental work tried to compare the widening effects of the above drugs on a rat induced HR protocol. They were tested by calculating the serum PDW levels augmentation.

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 Westar rats, the 7 days pre-experimental ad labium diet, the non-stop intra-experimental anaesthesiologist techniques, the acidometry, the electrocardiogram and 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, reoxygenation of 60 min was followed in group A; reoxygenation of 120 min in group B; immediate Epo intravenous (IV) administration and reoxygenation of 60 min in group C; immediate Epo IV administration and reoxygenation of 120 min in group D; immediate U-74389G IV administration and reoxygenation of 60 min in group E; and immediate U-74389G IV administration and reoxygenation of 120 min in group F. The dose height assessments for both drugs are described at preliminary studies as 10 mg/Kg body mass.

Hypoxia 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 reoxygenation. After exclusion of the blood flow, the protocol of HR was applied, as described above for each experimental group. The drugs were administered at the time of reperfusion; through inferior vena cava catheter. The PDW levels (PDWl) were determined at 60 th min of reoxygenation (for A, C and E groups) and at 120th min of reoxygenation (for B, D and F groups). However, a very weak relation was raised between PDWl with animals' mass (p-value=0.4240).

Statistical Analysis

Table 1 presents the (%) widening influence of Epo regarding reoxygenation time. Also, Table 2 presents the (%) widening influence of U-74389G regarding reoxygenation 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].

Table1. *The (%) widening influence of erythropoietin in connection with reoxygenation time*

Wider	±SD	Reoxygenation time	p-value
+1.60%	±2.82%	1h	0.0765
+1.36%	±2.40%	1.5h	0.0205
+1.13%	±2.00%	2h	0.1152
-1.67%	±1.96%	Reperfusion time	0.0026
+0.39%	±0.37%	interaction	0.2830

Table2. *The (%) widening influence of U-74389G in connection with reoxygenation time*

Wider	±SD	Reoxygenation time	p-values
+1.11%	±3.05%	1h	0.2368
+1.80%	±3.71%	1.5h	0.0314
+2.49%	±4.32%	2h	0.0807
-0.74%	±3.16%	reperfusion time	0.3280
+0.97%	±0.49%	interaction	0.0396

Table3. *The U-74389G / erythropoietin efficacies ratios on PDW levels widening after chi-square tests application*

Odds ratio	[95% Conf. Interval]		p-values	Endpoint
0.6940233	0.692697	0.6953522	0.0000	1h
1.319118	1.31679	1.321449	0.0000	1.5h
2.206972	.203064	2.210888	0.0000	2h
2.2484006	2.2435464	2.2532657	0.0000	reperfusiontime
2.458888	2.451713	2.466085	0.0000	interaction

Table4. *A U-74389G / erythropoietin efficacies ratios meta-analysis on 4 hematologic variableς (3 variables with balancing efficacies and 1 variable with opposite efficacies).*

Endpoint Variable	1h	p-value	1.5h	p-value	2h	p-value	Reperfusion time	p-value	interaction	p-value
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
Creatinine	168.9034	0.0000	4.872332	0.0000	3.039572	0.0000	1.0262016	0.0000	5.005523	0.0000
Mean	20.1929009	0.0000	4.33262345	0.0000	6.29145057	0.0000	1.08773713	0.0728	4.98048231	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
Platelet crit	-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

RESULTS

The successive application of chi-square tests revealed that U-74389G widened the PDWl by 0.6940233-fold [0.692697-0.6953522] than Epo at 1h, by 1.319118-fold [1.31679-1.321449] at 1.5h, by 2.206972-fold [2.203064-2.210888] at 2h, by 2.2484006-fold [2.2435464-2.2532657] without drugs and by 2.458888-fold [2.451713-2.466085] whether all variables have been considered (p-value=0.0000).

DISCUSSION

The unique available study investigating the widening effect of U-74389G on PDWl 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 peroxidative damage but hardly penetrates the blood-brain barrier. It elicits a beneficial effect in ototoxicity and Duchenne muscular dystrophy. It increases γGT, SOD, and 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 widening effect of Epo preparations in non iron deficient individuals. Ulu S et al calculated[3] the PDWl significantly higher in patients with nasal septal deviation strongly associated with obstructive and hypoxic manifestations. Unlu I et al[4] related the increase in PDW values with an increase in the risk of cardiopulmonary complications of nasal obstruction - a common cause of marked nasal septal deviation strongly related with hypoxia. Simsek G et al found decreased PDW values in groups that underwent operation for chronic hypoxia due to upper airway obstruction caused[5] by adenotonsillar hypertrophy being the most common cause of obstructive sleep apnea in children. Hou J et al claim that hypoxia can affect[6] platelet function. Along, only females with low PDWl were at greater risk for having low PDW (OR=1.34, ptrend<0.001) in the highest BMI groups, than those who had low PDWl in the corresponding lowest BMI group. The change of PDWl seems more sensitive than MPV ones to oxidative stress and hypoxia in Chinese female adults.

Song YJ et al associated[7] the indicator of platelet activation PDW with obstructive sleep apnea syndrome (OSAS) severity, the AHI (p-values < 0.001) and the Epworth sleepiness scale (p-values <0.05) which may increase the risk of cardiovascular disease (CVD). Sun J et al revealed[8] the platelet count of patients with TBI in plateau area 85.71% lower (p<0.05) than plain area in patients with traumatic brain injury (TBI). Haddad J Jr et al examined[9] the effect of intraperitoneal injections of 40 mg/kg of the U-74389G every 12 hours, on acute otitis media in guinea pigs. Streptococcus pneumonia organisms were inoculated into the right tympanic cavity; with the left ear served as a control one.

According to above, table 3 shows that U-74389G widened by 2.458888-fold [2.451713-2.466085] the PDWl than Epo (p-value=0.0000); a trend accentuated along time, in Epos non-deficient rats. A meta-analysis of these ratios from the same experiment, for 3 other seric variables, provides comparable results (table 4).

CONCLUSION

The anti-oxidant capacities of U-74389G widened by 2.458888-fold [2.451713-2.466085] the PDWl than Epo (p-value=0.0000) in rats. Along, this trend is accentuated along the short term time frame of the experiment.

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