Comparison of the excretory capacities of erythropoietin and U-74389G concerning serum creatinine levels

Comparación de las capacidades excretoras de eritropoyetina y U-74389G respecto a los niveles de creatinina sérica

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Abstract

Introduction  This study compared the excretory effects, the erythropoietin (Epo) and antioxidant drug U-74389G exert on serum creatinine levels through kidneys. 2 preliminary studies were used for this purpose including respectively one drug used in a renal ischemia–reperfusion (IR) protocol of an animal model. The preliminary studies are part of the present work. The subjects were pretreated in preliminary studies but the results of the same subjects were simply compared in the current work.

Materials and methods  The serum creatinine levels were evaluated at the 60th reperfusion min (for groups A, C and E) and at the 120th reperfusion min (for groups B, D and F) after IR in the 60 rats. Groups A and B received no drugs, rats from groups C and D were administered with Epo, whereas rats from groups E and F were administered with U-74389G.

Results  The first preliminary study recommended a non-significant excretory effect of Epo (p-value $= 0.4430 > 0.05$) than placebo for serum creatinine levels. The second preliminary study proved a very significant excretory effect of U-74389G (p-value $= 0.0005 < 0.05$) than placebo for serum creatinine levels. These 2 studies were co-evaluated since they came from the same experimental setting. The outcome of the co-evaluation was that
Introduction

The short-term excretory action of U-74389G is significant (p-value = 0.0005 < 0.05) than placebo for serum creatinine levels. U-74389G is a novel antioxidant factor. It implicates just only 255 known biomedical studies at present. 18.03% of these studies concern tissue ischemia and reperfusion (IR) experiments. The promising effect of U-74389G in tissue protection has been noted in these IR studies. U-74389G or also 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 which prevents both arachidonic acid-induced and iron-dependent lipid peroxidation. It protects against IR injury in animal heart, liver and kidney models. These membrane-associating antioxidants are particularly effective in preventing permeability changes in brain microvascular endothelial cells monolayers. However, the excretory capacity of U-74389G gets more comprehensible whether is compared with the same capacity of a standard known drug. Erythropoietin (Epo) is one of the more well studied and popular drug in hemodialysis (HD) medicine. However, the excretory action of Epo was proved non-significant (p-value = 0.4430 > 0.05) than placebo for serum creatinine levels. Actually, Epo implicates over 29,309 known biomedical studies at present. 3.46% at least of these studies concern tissue IR experiments. Although Epo is frequently used in HD medicine, just few related comparative drug reports were found in bibliography.

Materials and methods

Animal preparation

The Vet licenses of the research were provided under 3693/12-11-2010 and 14/10-1-2012 decisions. The granting company and the place of the experiment are mentioned in...
Comparison of the excretory capacities of erythropoietin and U-74389G

The ischemia was caused by laparotomic clamping inferior aorta over the renal arteries with forceps for 45 min. Reperfusion was induced by removing the clamp and restoration of the inferior aorta patency. The drugs were administered at the time of reperfusion; through an inferior vena cava catheter. The creatinine 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). The dose height selection criteria of Epo and U-74389G were assessed at immediate Epo IV administration and reperfusion for 120 min (group F); immediate U-74389G IV administration and reperfusion for 120 min (group D); immediate U-74389G IV administration and reperfusion for 60 min (group E); immediate U-74389G IV administration and reperfusion for 120 min (group F). The (%) excretory capacities

### Statistical analysis

- Table 1 presents the (%) excretory superiority of Epo than placebo regarding reperfusion endpoints. Also, - Table 2 presents the (%) excretory superiority of U-74389G than placebo regarding reperfusion endpoints. The chi-square tests were applied, in order the above superiorities to be compared; using the ratios which produced the (%) results per endpoint. The outcomes of chi-square tests are depicted in - 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 the excretory capacity of U-74389G was superior than that of Epo by 168.9034-fold [164.4292–173.4992] at 1 h, by 4.872332-fold [4.865416–4.879259] at 1.5 h, by 3.039572-fold [3.029025–3.050157] at 2 h, by 1.0262016-fold [1.0243103–1.0280964] without drugs and by 5.005523-fold [4.996097–5.014967] whether all variables have been considered (p-value = 0.0000).

### Discussion

The same authors reviewing 12 clinical trials, found lukewarm, non-significant, confusing and inconsistent excretory results for serum creatinine levels. Furthermore, Elshiekh et al. documented decreased plasma creatinine levels after treatment with recombinant human Epo (rhEpo) 5000 IU/kg intraperitoneally (IP) administered 30 min before renal IR or ischemic preconditioning (IPC) in male Wistar rats. Cakiroglu et al. calculated a non-significant tendency of serum creatinine levels for renal function improvement; particularly after daily Epo application at a concentration of 500 U/kg shortly after renal 30 min IR in rats. Kalantz et al. did not correlate serum creatinine levels with the two peaks of serum Epo levels although the serum creatinine levels reduction preceded the rise of Epo levels in patients after successful renal transplantation. Hernández-Navarrete et al. noticed stable serum creatinine levels and glomerular filtration at

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**Table 1** The (%) excretory influence of erythropoietin in connection with reperfusion time. Significant p-values when being <0.05

<table>
<thead>
<tr>
<th>Decrease</th>
<th>±SD</th>
<th>Reperfusion time</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10%</td>
<td>±9.78%</td>
<td>1 h</td>
<td>0.9904</td>
</tr>
<tr>
<td>4.84%</td>
<td>±5.78%</td>
<td>1.5 h</td>
<td>0.3721</td>
</tr>
<tr>
<td>9.59%</td>
<td>±7.74%</td>
<td>2 h</td>
<td>0.1509</td>
</tr>
<tr>
<td>−4.84%</td>
<td>±5.78%</td>
<td>Reperfusion time</td>
<td>0.3549</td>
</tr>
<tr>
<td>2.62%</td>
<td>±3.49%</td>
<td>Interaction</td>
<td>0.4430</td>
</tr>
</tbody>
</table>

**Table 2** The (%) excretory influence of U-74389G in connection with reperfusion time. Significant p-values when being <0.05

<table>
<thead>
<tr>
<th>Decrease</th>
<th>±SD</th>
<th>Reperfusion time</th>
<th>p-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.96%</td>
<td>±8.71%</td>
<td>1 h</td>
<td>0.0663</td>
</tr>
<tr>
<td>21.02%</td>
<td>±5.06%</td>
<td>1.5 h</td>
<td>0.0001</td>
</tr>
<tr>
<td>26.09%</td>
<td>±6.12%</td>
<td>2 h</td>
<td>0.0003</td>
</tr>
<tr>
<td>−4.20%</td>
<td>±6.12%</td>
<td>Reperfusion time</td>
<td>0.4103</td>
</tr>
<tr>
<td>11.69%</td>
<td>±3.16%</td>
<td>Interaction</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

**Table 3** The U-74389G/erythropoietin excretory efficacies ratios on serum creatinine levels after chi-square tests application. Significant p-values when being <0.05

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>[95% Conf. interval]</th>
<th>p-Values</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>168.9034</td>
<td>164.4292–173.4992</td>
<td>0.0000</td>
<td>1 h</td>
</tr>
<tr>
<td>4.872332</td>
<td>4.865416–4.879259</td>
<td>0.0000</td>
<td>1.5 h</td>
</tr>
<tr>
<td>3.039572</td>
<td>3.029025–3.050157</td>
<td>0.0000</td>
<td>2 h</td>
</tr>
<tr>
<td>1.0262016</td>
<td>1.0243103–1.0280964</td>
<td>0.0000</td>
<td>Reperfusion time</td>
</tr>
<tr>
<td>5.005523</td>
<td>4.996097–5.014967</td>
<td>0.0000</td>
<td>Interaction</td>
</tr>
</tbody>
</table>
Table 4 A U-74389G/erythropoietin efficacies ratios meta-analysis on 2 hematologic variables.22 Significant p-values when being <0.05

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Variable</th>
<th>1 h</th>
<th>p-Value</th>
<th>1.5 h</th>
<th>p-Value</th>
<th>2 h</th>
<th>p-Value</th>
<th>Reperfusion time</th>
<th>p-Value</th>
<th>Interaction</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>38.424</td>
<td>0.0000</td>
<td>9.076658</td>
<td>0.0000</td>
<td>6.222898</td>
<td>0.0000</td>
<td>1.001356</td>
<td>0.2184</td>
<td>12.66419</td>
<td>0.0000</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.981984</td>
<td>0.0000</td>
<td>4.085620</td>
<td>0.0000</td>
<td>9.051487</td>
<td>0.0000</td>
<td>1.119875</td>
<td>0.1092</td>
<td>4.968008</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

24 months in post-transplant patients underwent 52.3 months pre-transplant peritoneal dialysis. Gardner et al. used plasma creatinine levels to predict histopathological injury at 2 h after renal 40-min/48-h I/R; on renoprotective administration of Epo (1000 iu/kg IV) or remote IPC in a porcine model. Ahmadiasl et al. decreased creatinine levels after pre-treatment with Epo (5000 U/kg, IP) before 45 min/24 h renal I/R in male Wistar Albino rats. Wu et al. estimated a blood protein/creatinine levels ratio decreased by helix B surface peptide (HBSP) 8 nmol/kg derived from Epo; 2 weeks after 45 min/2 week renal I/R in a rat model. Kim et al. showed no significant differences on the incidence of post-operative acute kidney injury (AKI) defined as an increase in serum creatinine >0.3 mg/dl or >50% from baseline after pre-emptive Epo administration 300 IU/kg IV in patients. Li et al. showed a modest effect in preventing lipopolysaccharide (LPS)-induced elevation of creatinine levels and protecting against injured ultrastructure in the kidneys 24 h after rhEpo treatment (5000 U/kg) in AKI male Wistar rats. Han et al. attenuated the renal damage, the necrotic injury and the peak plasma creatinine levels after injection of mice adult renal progenitor cells (MRPC) which exhibit features consistent with renal stem cells; especially MRPC/Epo and MRPC/suramin in IR AKI male C57BL/6 mice. Matějková et al. found no differences after carbamylated Epo-FC fusion protein (cEpo-FC) (50 μg/kg), rhEpo (5000 IU/kg), or vehicle prior to 120 min/4 h I/R injury between treatment groups in pigs with atherosclerosis.4 Ardalan et al. found lower creatinine levels in renal IR + Epo group than only renal IR group (p < 0.05) after renal 30 min/24 h I/R in male Wistar rats. Ulusoy et al. found that creatinine significantly increased signal peptide-CUB (complement C1r/C1s, Uegf, and Bmp1)-EGF (epidermal growth factor-domain-containing protein 1 SCUBE1) levels higher in a HD group than a control (p = 0.000) one. Imamura et al. evaluated cEpo and Epo-treated IR rats had improved serum creatinine levels than saline-treated remnant kidney IR model rats. Rodrigues et al. preserved creatinine clearance and tubular function after pretreatment with continuous Epo receptor activator (CERA) in a sepsis-induced AKI model. Oba et al. found that Epo administration significantly inhibited the increase in blood creatinine levels after renal IR injury than control mice. Hu et al. exhibited lower serum creatinine levels and limited tubular necrosis 24 h after Epo administration in induced renal IR of male Sprague-Dawley rats.20 Chrysikos et al. did not find significantly different serum creatinine levels after U-74389G IV injection after pancreatic IR encompassing IPC 30 min/120 min in pigs.

According to above, Table 4 shows that U-74389G has at least 5-fold excretory capacity than Epo (p-value = 0.0000). A more detailed molecular and biochemical investigation of this excretory potency must be hold in order to elucidate the U-74389G molecular action mechanism.

Conclusion
The nephrologists and urologists must be informed about the effective excretory potencies of U-74389G when treat HD patients.

Ethical disclosures
Protection of human and animal subjects
The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data
The authors declare that no patient data appear in this article.

Right to privacy and informed consent
The authors declare that no patient data appear in this article.

Conflict of interests
The authors declare that they have no conflicts of interest.

References


