DEVELOPMENT OF AN EXPERIMENTAL MODEL OF TRIPLE WHAMMY PRE-RENAL ACUTE KIDNEY INJURY

Prieto-García L.[1,3], Sancho-Martínez SM.[1,3], Blanco-Gozalo V.[1,3], Quiros-Luis Y.[1,3], López-Novoa JM.[1,3], López-Hernández FJ.[1,2,3]

[1]Translational Research on Renal and Cardiovascular Diseases (TRECARD), Department of Physiology and Pharmacology, University of Salamanca, Salamanca, Spain.[2]Instituto de Estudios de Ciencias de la Salud de Castilla y León (IECSCYL), Research Unit, University Hospital of Salamanca, Salamanca, Spain. [3]Salamanca Institute for Biomedical Research (IBSAL), University Hospital of Salamanca, Salamanca, Spain.[4]Developmental Biology and Cancer, Institute of Child Health, University College London, UK.

Introduction

Pre-renal acute kidney injury (AKI) results from glomerular haemodynamic alterations leading to reduced glomerular filtration rate (GFR) with no parenchymal compromise. Renin-angiotensin system inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor antagonists (ARAs), non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics, are highly prescribed drugs that are frequently administered together. Double and triple associations have been correlated with increased pre-renal AKI incidence, termed “double whammy” and “triple whammy” respectively.

Aims

Accordingly, our main goal is to set up an experimental animal model that replicates this clinical situation. This achievement would be the first step to further research on pathophysiological mechanisms involved in pre-renal AKI in order to improve its diagnosis and prevention.

Methods/ experimental design

Diuretics, NSAIDs and angiotensin II inhibitors drugs were administered in single, double and triple therapy to Wistar rats in non-nephrotoxic doses. In relevant groups, NSAID and ACEi were given to animals during 10 days and furosemide was added at the fourth day of the treatment regimen (figure 1). Urine and blood samples were collected every two days and their kidneys were removed after perfusion at the end of the experiment. We analysed their renal function (plasma creatinine, plasma urea, N-acetyl-glucosaminidase excretion, proteinuria…) and renal histological alterations through eosin-hematoxylin staining.

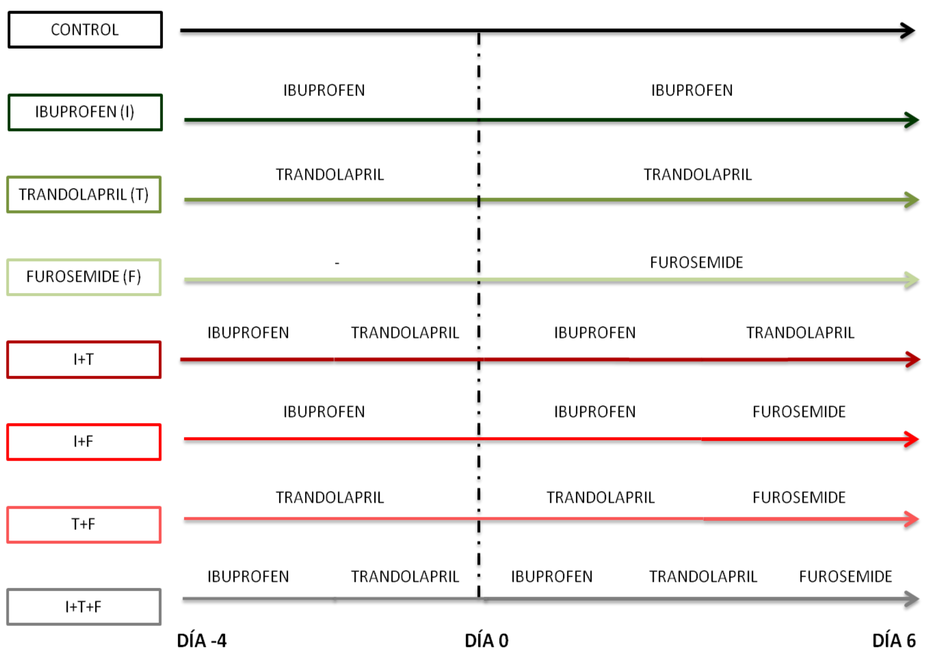


Figure 1. Schematic image of the experimental animal model of Triple whammy pre-renal AKI. Green colours represent single therapies (ibuprofen, trandolapril or furosemide administered alone) , red colours indicate double treatment (I+T, I+F, T+F) and grey colour labels triple treatment group.

Conclusions

Plasma creatinine and plasma urea were increased in rats treated with the triple therapy. However, these renal function alterations were not detected in single and double treatment groups. Moreover, other renal function parameters and renal histology were not altered in rats treated with this three-drugs combination. Our results show that our experimental animal model recreates a pre-renal AKI due to renal hemodynamic alteration without renal parenchymal damage.

Results

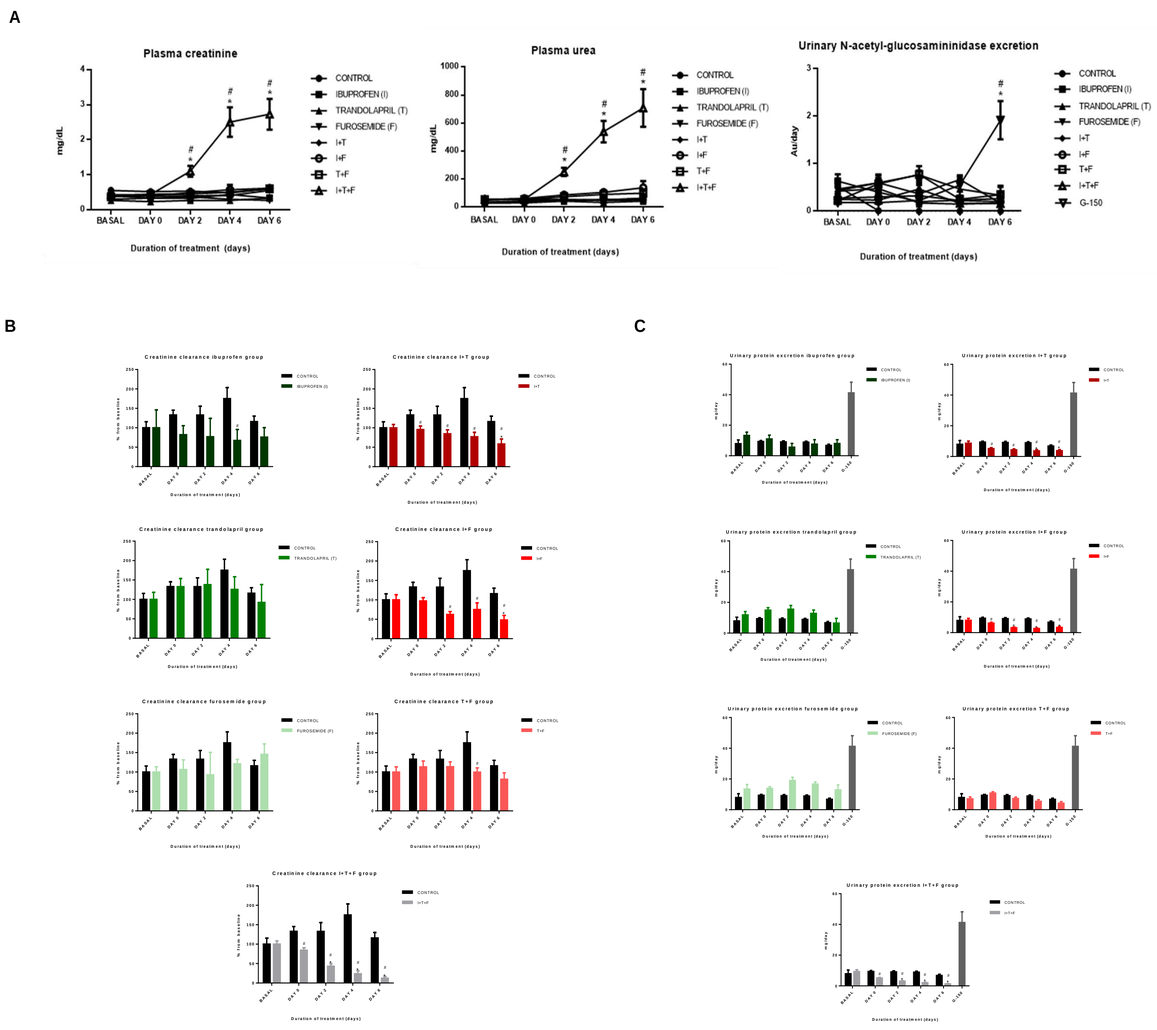
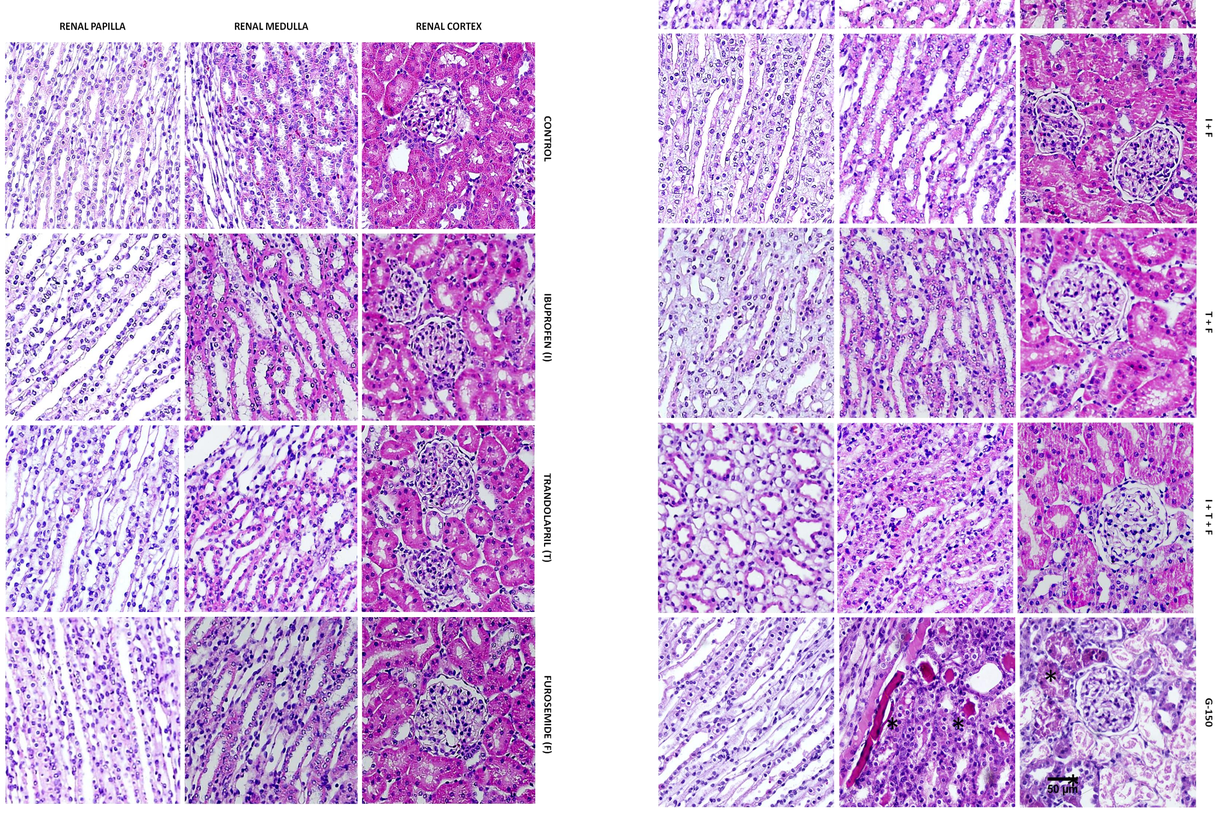


Figure 2. Renal function assessment in single, double and triple therapy groups. Urine from rats treated with neprhotoxic doses of amynoglucoside gentamicin (G-150) was used as a positive control of an intrinsic renal injury . A) Plasma creatinine, plasma urea and urinary N-acetyl-glucosaminidase excretion ; B) Creatinine clearance and C) Urinary protein excretion. Data represents average ± SEM of n=10. *, p< 0.05 with respect to own basal sample in each group; # , p<0.05 with respect to the same day of treatment in control group.

Figure 3. Representative renal histology images of eosin-hematoxylin staining (20x). Cortex, medulla and papilla histologies were analysed in all groups. Kidney images from rats treated with nephrotoxic doses of gentamicin (G-150) were used as a positive control group . * labels renal histologic alterations detected.



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